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AGE AND POLYPLOIDY OF RAT LIVER NUCLEI AS MEASURED BY VOLUME AND DNA CONTENT

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It is generally accepted that polyploidy of hepatic cell nuclei occurs in several mammalian species. Evidence for this includes the presence of interphase hepatic nuclei with increased volumes (7, 13, 15, 27, 29, 32, 38, 43) and DNA content (33, 34, 35, 39, 40, 41). Both of these measures fall into discrete frequency classes whose means form a geometric series 2:4:8, etc. (21, 22, 23, 30, 31, 34, 35, 39). This suggests a successive doubling of chromosome number, which in a few instances has been confirmed by chromosome counts (8, 14, 25). In addition, the mean DNA per nucleus is usually higher in adult mammalian liver than in other somatic tissues (17).

Although there is good evidence that hepatic polyploidy increases in the rat (11, 24, 26, 33), mouse (30), and man (39) during growth, the data on changes during senescence are scanty (28). Andrew and his co-workers (3) have reported an increase in the average nuclear diameter of hepatic cells during senescence in the mouse, as well as the presence of very large deeply staining nuclei (2, 3). Observations on a small number of humans (4 subjects aged 18-21 years and 4 subjects aged 40-90 years) utilizing Feulgen microspectrophotometry suggest a slightly higher average DNA content of hepatic nuclei in the livers of the old subjects ($P = 0.05$). However, the average volume of hepatic nuclei was not significantly higher in the older individuals (39).

No estimates of the incidence of exceptionally large nuclei in the total nuclear population have been made. It is the purpose of the present study to estimate this incidence in the liver of the rat and to compare with age two quantitative measures of the average degree of hepatic polyploidy: 1) average volume of hepatic nuclei and 2) mean DNA per nucleus.

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MATERIALS AND METHODS

Animals. Thirty-eight unmated male and female rats of the McCollum strain were used. These were of two age levels: 12 to 14 and 24 to 27 months or "adult" and "old" animals, respectively. This age span was intended to exclude growth changes from a study primarily concerned with senescence (4). The rats were housed 5 to a cage (60 x 36 x 37 cm.) in quarters maintained at 75 ± 2 F. and were given water and a standard stock diet (5) *ad libitum.*

Preparative Method. Nuclei were prepared by a citric acid technique adapted from Dounce (18) and Boivin and associates (9) with an additional layering modification (42). Each rat was sacrificed by stunning and decapitation and the liver rapidly removed, chilled in a Petri dish surrounded by crushed ice, and weighed. A sample of approximately 1 Gm. was excised from the left lobe and homogenized for 20-30 sec. in about 5 ml. of ice cold 0.04 M citric acid with a motor-driven teflon pestle and a 15 ml. glass tube. Unless otherwise stated, all subsequent dilutions in the preparative procedure were made with 0.04 M citric acid and the temperature was maintained at 0-4 C. The homogenate was mixed and diluted to 30 ml. of which 4 ml. were taken for microscopic examination. The remaining homogenate was filtered first through coarse gauze and then through fine flannelette and finally diluted to 40 ml. This was divided into four 10 ml. aliquots, each of which was layered over 30 ml. of 0.04 M citric acid containing 5% sucrose in a 40 ml. conical tube. The tubes were centrifuged 10 minutes with a force gradient of $273 \times g$ at meniscus and $500 \times g$ at the bottom of the tube.* An additional one minute was allowed for each 1000 rpm acceleration and deceleration

* 1500 rpm, International Equipment Co. Head #269 with a PR-1 refrigerated centrifuge.

to avoid stirring at the interface. This technique retained most of the brown debris in the top 10 ml. of the supernate but allowed nuclei to sediment freely. The entire supernate was decanted and the nuclear sediments resuspended, pooled, and diluted to 40 ml. The above layering and centrifugation was repeated twice. Almost no turbidity remained in the supernate after the third centrifugation. Final sediments were pooled.

As sucrose in a concentration of 5% interfered with the analysis of DNA, it was removed from the pooled nuclear sediment by three centrifugal washings in 15 ml. of 0.04 M citric acid (10 minutes each, 1500 rpm, 200-465 × g). The adequacy of this washing procedure was established in a separate series of experiments. The final sediment was diluted to 5.0 ml. and filtered through fine flannelette to remove any remaining aggregated nuclei. A 4.0 ml. aliquot of this filtrate was frozen for DNA analyses and the remainder used for counting. Microscopically, the nuclei were generally undistorted and nearly free of debris (fig. 1).

Total Nuclear Counts. The undiluted suspension was counted in haemocytometer chambers (Spencer Bright-Line, Neubauer ruled, 0.1 mm. deep) at 430 × magnification. The central 0.1 mm.^{3} or red cell volume was used. Enough suspension was introduced with small tipped (not capillary) glass pipettes to just fill the chambers, at least 4 of which were counted for each preparation.

Estimation of DNA. Nucleic acids were precipitated, washed, and hydrolyzed by the Schneider procedure (36) and DNA concentration determined by the Stumpf colorimetric method (37).

Differential Counts. Differential counts were performed simultaneously with the total counts on all washed suspensions. With an ocular micrometer scale as a reference standard, nuclei were classified as "hepatic" (minor axis* $>$ 6.5μ) or "small" (minor axis $\leqq$ 6.5μ). This is not arbitrary but is based upon the bimodal distribution of nuclear diameters in both sections and homogenates of liver (19, 20). By this criterion the small class of nuclei is derived mainly from stromal elements, but also contains a small proportion of probable diploid hepatic nuclei (7, 15, 20, 23, 27, 31, 39). For this reason such nuclei are termed "small" rather than "stromal." Nuclei of polymorphonuclear leukocytes were separately tallied but comprised only about 1% of the total.

* Diameter perpendicular to the greatest diameter.

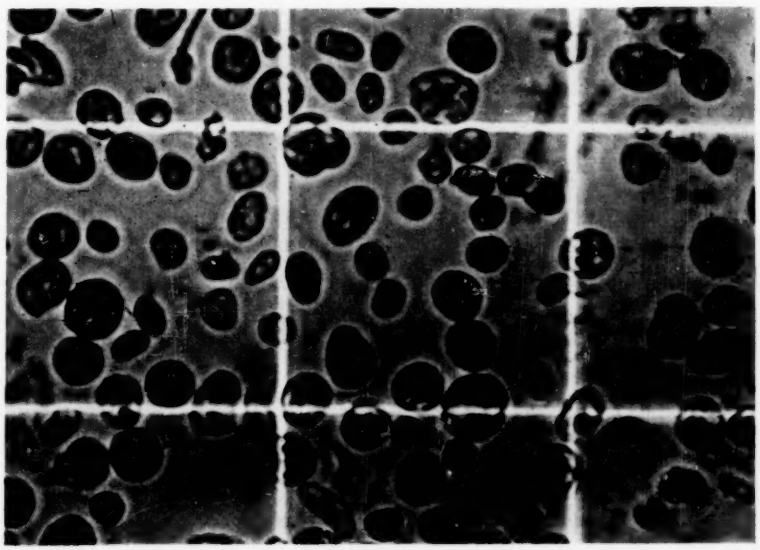

Fig. 1. Washed liver nuclei in a counting chamber. Note two main size classes and several leukocyte nuclei. Unstained, in 0.04 M citric acid; distance between grid lines = 50μ.

Measurements in Tissue Sections. Liver samples from 33 of the 38 animals were fixed in 10% formalin, dehydrated, and embedded in the usual manner. Serial sections were cut at 7μ and stained with hematoxylin and eosin.* Incidence of giant hepatic nuclei was tabulated by scanning ten 430 × fields per rat (approximately 200 nuclei per field). Nuclei with minor axes of $> 10\mu$, $< 15\mu$ and those with minor axes $\geqq 15\mu$, were separately tallied with the aid of an ocular micrometer scale calibrated to read directly in μ.

The same micrometer and magnification were used to determine *average* volume of hepatic nuclei. Twenty-five hepatic nuclei per rat were randomly selected from all lobular zones. The major and minor axis of each nucleus were measured to the nearest 0.5μ and used to calculate volume by a prolate spheroid assumption. The 25 volumes were averaged to give the mean volume per hepatic nucleus for each rat (table 1). No correction was applied for size underestimation due to sectioning.

RESULTS AND DISCUSSION

Reliability of Methods. Counts in the first two chambers were compared to counts in the second two to determine the standard error of estimate (N = 38). This was 6.0% of the mean value for total nuclei contained in each pair of chambers. Counts in wire loop filled and pipette filled chambers were not significantly different (1).

The standard error of the estimate for 20 duplicate DNA determinations was 7.7% of the mean for this subsample. As centrifugation adequate to sediment microscopically visible particles* left only 3.2% of the total homogenate DNA in the supernate, it was concluded that loss of soluble DNA from intact nuclei was negligible.

Mean DNA Per Nucleus Values. No age or sex differences in the mean DNA per nucleus were observed (table 1). However, this value is affected not only by polyploidy of hepatic nuclei but by the presence of small nuclei in the suspensions analyzed. In another study (20), small (mainly stromal) nuclei were separated from hepatic by continuous density gradient sedimentation. Mean DNA per nucleus values were 7.32 ± 0.22† $\mu\mu$g. for small nuclei, 14.3 ± 0.45 $\mu\mu$g. for hepatic or approximate diploid and tetraploid values, respectively. A more precise value for small nuclei was estimated by correcting for the slight contamination of this fraction with large hepatic nuclei. This value (6.7$\mu\mu$g.) is very close to those reported by Davidson (16) for a variety of diploid mammalian tissues. From these findings it is apparent that an age increase in the polyploidy of hepatic nuclei could be masked by simple

* We are indebted to Dr. Warren Andrew for preparation of histological sections.

* Ten minutes at 11,400 rpm, head #40, Spinco Model L Preparative Ultracentrifuge.

† Standard error of the mean.

TABLE 1. ESTIMATES OF POLYPLOIDY AND DIFFERENTIAL COUNTS IN LIVER OF RATS.

	Sex	Body Weight (Gm.)	Liver Weight (Gm.)	Estimates of Polyploidy: Mean DNA/ Nucleus ($\mu\mu$g.)*	Mean Volume† of Hepatic Nuclei in Sections (μ^3)	Giant Hepatic Nuclei in Sections; Total Nuclei Observed with Minor Axes of: >10μ <15μ	15μ and >	Differential Counts (% in Washed Suspensions): Large Nuclei (Hepatic)	Small Nuclei	Polymorpho-nuclear Leukocyte Nuclei
		Mn. σmn.	Mn. σmn.	Mn. σmn.	Mn. σmn.			Mn. σmn.	Mn. σmn.	Mn. σmn.
Young	F	243 3.9	7.97 0.24	11.8 0.43	168 7.2	0	0	72.4 1.16	26.7 1.07	0.9 0.11
N		9	9	9	7	7	7	9	9	9
Old	F	282 9.2	9.42 0.28	12.6 0.44	210 22.0	30 (in 3 rats)	3 (in 1 rat)	68.3 1.55	30.6 1.53	1.1 0.15
N		10	10	10	8	8	8	10	10	10
Young	M	470 21.9	13.29 0.91	11.9 0.42	190 6.0	7 (in 5 rats)	0	72.7 0.55	26.4 0.48	0.9 0.11
N		9	9	9	9	9	9	9	9	9
Old	M	433 8.2	13.05 0.52	11.9 0.53	191 6.1	4 (in 4 rats)	0	71.5 0.92	27.4 0.86	1.1 0.10
N		10	10	10	9	9	9	10	10	10
Total	.....	.....	.....	12.0 0.23	190 6.3	41 (in 12 rats)	3 (in 1 rat)	71.2 0.61	27.8 0.59	1.0 0.02
N	.....	.....	.....	38	33	33	33	38	38	38

* 10^{-12} Gm.

† Calculated as prolate spheroids.

dilution if the proportion of small nuclei increased concomitantly. Since such an increase was actually observed in female rats ($P = .05$, table 1), the following equation was used to estimate the true DNA content per hepatic nucleus:

$$D_h = \frac{D_m - D_s(S + P)}{H}$$

where D_h = calculated mean DNA per hepatic nucleus; D_m = observed mean DNA per nucleus; D_s = mean DNA per small nucleus (6.7 $\mu\mu$g.); S = observed proportion of small nuclei; P = observed proportion of polymorphonuclear leukocyte nuclei and H = observed proportion of hepatic nuclei. Although D_m values were slightly higher in old female than in young female rats ($P = > .05 < .10$), there was no change with age in the males. No significant sex differences in this value were found.

The difference in DNA content between small and hepatic nuclei is also important for another reason. In a previous series of 35 rats, the percentage of hepatic nuclei was 55.5 ± 0.76 and 60.1 ± 0.87 for whole homogenates and washed nuclei, respectively. This difference is highly significant ($P < 0.001$, paired data). In the present study, more washings were used and, as expected, the proportion of hepatic nuclei was further elevated to a level higher than that of intact liver tissue (15). This selection of hepatic nuclei by repeated centrifugal washings would tend to elevate the absolute level of mean DNA per nucleus, but would also exaggerate rather than obscure any changes with age in the degree of polyploidy. The importance of this factor is not generally realized.

Results of the present study are in accord with previous estimates of the mean DNA per nucleus in rat liver in failing to demonstrate a change with senescence (24, 26) (table 2). The small discrepancies among the observations on old animals shown in table 2 may result from variation in nuclear selection characteristic of different preparative techniques as explained above. The only definite increase in mean DNA per nucleus occurs during growth of the rat, a finding consistent with Feulgen miscrospectrophotometry of individual hepatic nuclei. With the latter technique, Naora (33) found that the proportion of tetraploid nuclei reaches a maximum level (88% of hepatic nuclei) at a body weight of 100 Gm. but is remarkably stable thereafter. This result is in striking agreement with both the direction of change and absolute levels of mean DNA per nucleus seen in table 2.

Average Volume of Hepatic Nuclei. Esti-

TABLE 2. MEAN DNA PER LIVER NUCLEUS IN RATS OF DIFFERENT AGES.

Investigators	Sex	Age	Body Weight (Gm.)		Number	Mean DNA/Nucleus ($\mu\mu$g.)	
			Mn.	σmn.		Mn.	
Jacob, Mandel, and Mandel (26)	F	8 days	14.3	4.7	26	7.0*	
	F	14 days	26.4	3.2	17	7.4	
	F	30 days	66.0	6.5	11	9.0	
	F	60 days	129.0	14.0	8	10.2	
	F	"Adult"	219.0	51.0	16	13.0	
	F	2 years	243.0	45.0	7	13.2	
			Range			Mn.	
Fukuda and Sibatani (24)	..	.....	11.9	12.3	7	5.9	
	..	.....	24.9	25.2	4	5.1	
	M and F	.....	48.0	52.0	6	9.3	
	M and F	.....	96.0	100.0	6	11.1	
	M and F	.....	196.0	200.0	6	11.2	
	M	.....	320.0	355.0	3	11.4	
			Mn.	σmn.		Mn.	σmn.
Present Study	F	1 year	243.0	3.9	9	11.8	0.43
	F	2 years	282.0	9.2	10	12.6	0.44
	M	1 year	470.0	21.9	9	11.9	0.42
	M	2 years	433.0	8.2	10	11.9	0.53

* Calculated from DNA phosphorus on the basis of 9.23% phosphorus in sodium desoxyribonucleate (12).

TABLE 3. CALCULATED NUMBERS OF NUCLEI/GRAM OF LIVER TISSUE.

	Sex	Number	DNA/Gm. Wet Weight (mg.)*		Nuclei/Gram Wet Weight x 10^{-8}							
					Total		Large (Hepatic)		Small (Hepatic)		Polymorpho-nuclear Leukocyte	
			Mn.	σmn.	Mn.	σmn.	Mn.	σmn.	Mn.	σmn.	Mn.	σmn.
Young	F	9	3.29	0.09	283	14.4	204	8.7	76.2	6.19	2.7	0.45
Old	F	10	3.06	0.06	246	9.8	169	8.7	75.0	3.63	2.6	0.36
Young	M	8	3.04	0.17	260	21.1	189	14.3	68.7	6.42	2.6	0.52
Old	M	9	3.07	0.08	266	16.8	189	11.6	73.9	5.63	3.0	0.35
Total		36	3.12	0.05	263	7.7	187	5.6	73.6	2.65	2.7	0.20

* Data from Barrows, Yiengst and Shock (6) for the same animals as those employed in the present study.

mates of nuclear volume made in the present study formed a single definite frequency distribution (presumably tetraploid), with a suggestion of diploid and octoploid classes. The mean volumes were not significantly different with age or sex (table 1). In these respects they are consistent with other estimates of polyploidy and with previous measurements of nuclear size. In rat liver, average nuclear size does increase with growth (11, 32) but not with senescence (11, 38).

Giant Hepatic Nuclei. Differences with age or sex in the frequency of giant nuclei were not demonstrated, although the largest nuclei were found in washed suspensions and sections from an old female rat. Average nuclear volume ($344\mu^3$) and mean DNA per nucleus (15.1 $\mu\mu$g.) values for this animal were also the highest observed. A major purpose of these observations was to establish an order of magnitude for the frequency of giant hepatic nuclei from which their effects upon the mean DNA per nucleus could be estimated. The following approximation is based upon the known distribution of nuclear types in rat liver and the probable ploidy of these types (15, 20). If the DNA to volume relationship holds in the upper size range, a "supergiant" of 20μ diameter would probably be 64-128 ploid, with a DNA content on the order of 200-400 $\mu\mu$g. If the incidence of such nuclei increased from 0 to 1% with age, the mean DNA per nucleus should increase by 15-35%, a change detectable by chemical means. However, an increase with age to 0.1% (the order of magnitude observed in the present study) would produce only a 2-3% rise in the mean DNA per nucleus, a change within the range of error in the present investigation. It is concluded that giant nuclei are generally too infrequent to measurably affect mean DNA per nucleus results.

Cellular Composition of Liver. In biochemical studies a useful description of a tissue sample is the number of nuclei it contains (total or per unit wet weight). This is equal to the ratio of tissue DNA concentration to the mean DNA per nucleus and is most precisely and easily obtained if the latter is known to be stable under test conditions, as in rat liver with senescence. Our calculated values for the number of nuclei per gram wet weight are shown in table 3. In addition, these values have been multiplied by the differential count proportions (table 1) to give the number of nuclear types per gram. No age differences in the nuclear populations were observed in the livers of male rats. However, a slight decrease with age in the calculated total nuclei ($P = 0.05$) and hepatic nuclei ($P = 0.01$) per gram wet weight were seen in the female animals. We prefer not to attach much importance to these differences because of the large number of primary measures necessary to the computation of such derived values. Our mean value of 263×10^6 total nuclei per gram wet weight agrees reasonably well with results that may be calculated from data on fixed and stained sections (10, 33) but would tend to be slightly low because of the nuclear selection factor discussed above.

SUMMARY

Three estimates of polyploidy, i.e., 1) the chemically determined mean DNA per nucleus, 2) mean volume of hepatic nuclei and 3) frequency of giant hepatic nuclei, were applied to liver samples from 38 rats of both sexes and of two age levels, 12 to 14 and 24 to 27 months. No age or sex differences in these estimates of polyploidy were found. The mean DNA con-

tent was 12.0$\mu\mu$g. per nucleus for all groups of animals, the mean volume of hepatic nuclei was 190 $\pm$ 6.3μ^3 and the average incidence of giant nuclei was approximately 0.06% of total hepatic nuclei. It is concluded that in the adult rat of both sexes DNA analysis provides a stable measure of nuclear number and may be used as a basis for comparing metabolic functions of the liver in animals of different ages.

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THE LONGEVITY AND MORTALITY OF THOROUGHBRED STALLIONS

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In a previous paper (1) some life tables and survival curves for English thoroughbred mares were presented, based on the histories, extracted from the General Stud Book, of 1,492 animals foaled in 1875-1880 and 1,250 foaled in 1860-1864. The Stud Book contained no comprehensive lists of stallions for the same periods.

Three different estimates of stallion longevity from Stud Book sources have now been obtained. Two are based on cross-sectional samples and the third on the earliest single age-group for which a list of names could be obtained. All three groups of data leave a good deal to be desired, but it is possible to obtain from them some provisional indication of the rate at which the expectation of life of entire male horses declines with age, compared with that of mares. This does not seem to have been attempted previously.

METHODS AND RESULTS

The two cross-sectional samples were composed of (a) all the animals listed in vols. 1 and 2 (1910 and 1913) and (b) all the animals listed in vol. 5 (1921) of the *Register of Thoroughbred Stallions,* excluding names in the Appendix. Thirty-three animals from sample (a) were alive in 1921 and figure in both samples. Ages at death or disposal were obtained from the obituary lists in the *Register* and from the similar but not identical obituary of stallions in the *General Stud Book.* By combining information from these two sources it was possible in most cases to distinguish between deaths due to shooting, accident, and causes conventionally assigned as "natural," which were scored as for mares, all deaths from accident or deliberate destruction being treated as losses. This scoring convention is arguable, but it has been maintained here for consistency. Animals disappearing from the record were traced in the export lists of the *General Stud Book,* and some additional information was obtained from the records of premium and approved stallions in the *National Hunters and Light Horse Society* stud-book. Life-tables were then prepared by calculating age-specific death rates with allowance for entrants and leavers.

The cohort sample was obtained by taking, from the list of sires of brood mares in vols. 17 and 18 of the *General Stud Book,* all those foaled in 1880-1884 inclusive (N = 180). These were then traced through the records in the same way. Stallions appear in this list only when their daughters are entered as brood mares—some sires are already dead when this occurs, but this does not affect the resulting table, since once the names are known search for them can be made retrospectively. The total numbers in this sample were small (180 lives) of which 38 ended in conventionally "natural" deaths, none of them before the age of 8.

Table 1 gives the full table prepared for the two cross-sectional samples. It will be evident that no weight can be attached to the early values for mortality or to the early expectation of life, because of the lack of entrants at the start of the table and the different age distributions in the two samples. The object of computing the whole table was to obtain serial figures for the expectation of further life and its standard error for successive later ages. The cohort sample was similarly treated. The mean expectation of further life at 4, 10, 15, 20, and 25 years for all three samples of stallions and for the two samples of mares is compared in table 2, together with the standard errors obtained by Irwin's approximation (2).

DISCUSSION

It will be seen from table 2 that there is no significant difference at any age between the further life-expectancies of mares and those of stallions in the cohort sample, while the life expectancies of the two cross-sectional samples differ significantly from one another, from the mares, and from the cohort sample of stallions.

There are a number of ways in which these discrepant results could be treated. The cohort sample is closest in date and in method of selection to the sample of mares, but it depends on 38 conventionally "natural" deaths, none of them occurring under 8 years of age. The dis-

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TABLE 1. ABBREVIATED LIFE TABLES FOR THOROUGHBRED STALLIONS.

Age	Listed 1910–1913				Listed 1921			
	N	q_x	L_x	e_x	N	q_x	L_x	e_x
4	9	0.0	1.0000	17.71±0.84	2	0.0	1.0000	19.502±0.75
5	38	.0526	1.0000		12	0.0	1.0000	
6	73	0.0	.9474		30	0.0	1.0000	
7	126.5	.0079	.9474		38.5	.0260	1.0000	
8	162	0.0	.9399		56	.3570	1.0000	
9	195.5	.0102	.9399		63	0.0	.9740	
10	220	.0227	.9303	12.87±0.58	81.5	0.0	.9392	15.6 ±0.53
11	233.5	.0385	.9092		93	0.0	.9392	
12	240	.0208	.8742		111	0.0180	.9392	
13	244.5	.0123	.8560		112	.0268	.9223	
14	237.5	.0337	.8455		110.5	.0090	.8976	
15	217.5	.0276	.8170	9.31±0.59	115.5	.0087	.8895	10.13 ±0.50
16	201	.0199	.7945		110.5	0.0	.8817	
17	190.5	.0210	.7787		104	.0288	.8817	
18	176.5	.0453	.7623		97	.0619	.8563	
19	159.5	.0376	.7278		89	.0562	.8033	
20	146.5	.0956	.7004	5.41±0.64	74.5	.0402	.7582	6.28 ±0.47
21	122.5	.1061	.6344		58.5	.1026	.7277	
22	100	.1100	.5662		44	.0682	.6530	
23	71.5	.1399	.5039		35.5	.0282	.6085	
24	57	.1404	.4334		28.5	.1404	.5913	
25	43	.2093	.3726	3.01±1.11	18.5	.2162	.5083	3.05 ±0.52
26	27	.2222	.2946		10	.1000	.3984	
27	16.5	.2424	.2291		8	.2500	.3586	
28	11	.3636	.1736		6	.3333	.2690	
29	4	.2500	.1105		3	0.0	.1793	
30	2	0.0	.0829		2	1.0	.1793	
31	1	1.0	.0415				0.0	

agreement between the two cross-sections has not been concealed by combining them, since it is conceivable that it may include a real secular change, and there is a case for taking the 1910-1913 cross-section as the better, on grounds of size, partial duplication in the other sample, and the fact that it contains no intervals in the middle of the table where $q_x = 0$. In recent work on the mares foaled in 1900 and in 1910, we have found a significantly shorter life span than in the earlier samples.

Over most of the lifespan the plot of log q_x/t for both samples of mares is a presentable straight line with a doubling-time of $3\frac{1}{2}$-4 years. The true shape of the same curve for stallions cannot safely be inferred until more plausible data are available; most of the gain in male survival occurs over the years where mares most commonly die from causes connected with foaling. The only solid conclusion which can be drawn at present is that stallions are not shorter-lived than mares and may be a good deal longer-lived. Further data are being sought.

SUMMARY

Life tables obtained in different ways were prepared for 3 samples of thoroughbred stallions. These yielded discordant results, but the expectation of life of stallions at all ages from 4 years seems to be at least equal to, and possibly greater than, that of mares previously studied.

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TABLE 2. EXPECTATION OF FURTHER LIFE (YEARS) FOR THOROUGHBRED MARES AND STALLIONS AT DIFFERENT AGES. (MEANS AND STANDARD ERRORS).

Age	Stallions		Mares		
	Listed 1910–1913	Listed 1921	Foaled 1880–1884	Foaled 1860–1864	Foaled 1875–1880
4	17.71 (0.84)	19.50 (0.75)	17.29 (0.72)	17.04 (0.21)	17.31 (0.21)
10	12.87 (0.58)	15.60 (0.53)	11.95 (0.73)	11.82 (0.21)	11.90 (0.20)
15	9.31 (0.59)	10.13 (0.50)	8.08 (0.69)	7.80 (0.20)	7.98 (0.20)
20	5.41 (0.64)	6.28 (0.47)	5.01 (0.67)	4.54 (0.22)	4.76 (0.21)
25	3.01 (1.11)	3.05 (0.52)	2.83 (0.43)	2.54 (0.45)	2.60 (0.35)

STUDIES ON THE EFFECT OF HEAT AND AGE IN DECREASING ABILITY OF HUMAN COLLAGEN TO SWELL IN ACID*

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In a previous paper (1) it was shown that with increasing age, human diaphragm tendon loses its ability to swell in acid and alkaline solutions. There is little change in swelling from infancy to near the end of the third decade, followed by abrupt decrease in swelling ability between 30 and approximately 50 years, with a slow decline in swelling after 50 years. Pretreatment with heat caused young tendon to lose its swelling ability, and it was pointed out that this finding was consistent with the theory of Sinex (4) that aging of collagen *in vivo* results from thermal denaturation at body temperature.

The experiments described in the present report were carried out to investigate further the relationship of heat to aging of tendon as manifested by decreased swelling ability. In order to discover if the concentration of young expansible collagen decreases by conversion to old rigid collagen, rather than by accumulation in tendon of some non-expansible non-collagenous material, collagen and water content of tendon as a function of age were measured. The effect of heat on subsequent swelling ability as a function of age was determined consequent to the following reasoning: if conversion of young to old collagen is any order other than a zero order reaction, the rate of conversion should be proportional to the concentration of young collagen, and if the conversion can be accelerated by heat, the rate of loss of swelling ability at elevated temperatures should also be proportional to concentration of young collagen. In the course of these determinations it was found that tendon increased in weight on exposure in Ringer's solution to elevated temperature alone and that the rate and extent of this increase varied with age. Studies were carried out on this phenomenon.

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† U. S. Public Health Service Research Fellow in Pathology.

MATERIALS AND METHODS

Water content was determined by scraping fresh tendons free of loose tissue and weighing them before and after heating to constant weight at 92 C. Collagen content of fresh tendon was determined by the hydroxyproline method of Neuman and Logan (2). Water and collagen were expressed as percentage by weight of fresh tendon.

The source of tendons and method for determining swelling ability were as previously described (1). In the present experiments swelling ability was determined only in a pH 2.5 HCl solution because the changes related to age were most clearly shown at this pH.

First, tendon fragments were heated at 56 C. in mammalian Ringer's solution for 15, 30, and 60 minutes, after which they were cooled to room temperature and weighed. Changes in weight on heating alone for the various times were determined, after which swelling ability at pH 2.5 was ascertained at room temperature. Several tendons from representative age levels were tested in this way in order to compare heat effects as functions of age. Then, to determine maximum initial rate of heat effect, 65 tendons from infants to aged individuals were heated at 56 C. for 15 minutes, cooled to room temperature, and tested for swelling ability at pH 2.5. Eighty-nine tendons were heated at 56 C. for 15 and 30 minutes to determine effect of elevated temperature alone. Percentage increase in weight on heating alone and effect of heat in decreasing subsequent swelling ability in acid were calculated for each tendon. The latter was obtained by subtracting the percentage swelling at pH 2.5 after heating from the percentage swelling of unheated controls at pH 2.5.

RESULTS

Water and collagen content of tendon as a function of age are shown in figure 1. Neither varies significantly with age, although there is a questionable slight increase in collagen at

around 30 years of age. Together, collagen and water comprise about 90% of the tendon weight.

The effect of heat alone in causing water imbibition by tendons is shown in figures 2 and 3. Figure 2 indicates swelling versus time at 56 C. for tendons from representative age levels. In figure 3 percentage increases in weight on incubation for 15 and 30 minutes are plotted against age for 89 tendons. In the first two decades there is no lag period, and an increasing ability to swell is found to the age of about 20 years. Starting around the third decade the swelling curves become sigmoidal, with less swelling occurring in 15 minutes with increasing age. Swelling in 15 minutes is therefore a measure of extent of the lag period. However, extent of swelling by 30 minutes' incubation remains at a high level until around 50 years of age, after which there is a marked decrease in the ability to imbibe water. These phenomena are most clearly shown in figure 3 where

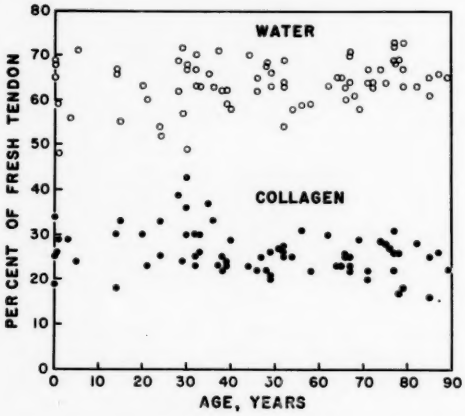

Fig. 1. Water and collagen content of fresh tendon as a function of age.

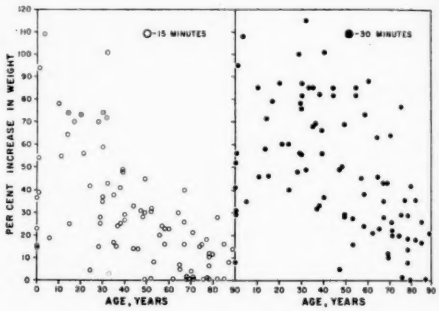

Fig. 3. Increase in weight of tendons on incubation at 56 C. for 15 and 30 minutes as functions of age.

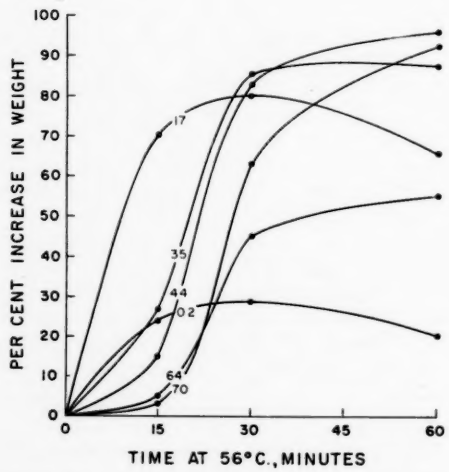

Fig. 2. Increase in weight of tendons from representative age levels on incubation at 56 C. Age in years is indicated for each curve.

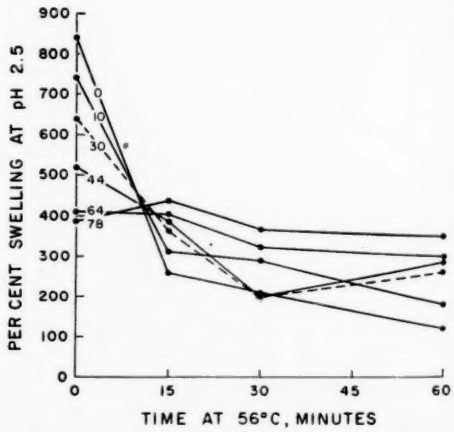

Fig. 4. Effect of exposure of tendons to 56 C. for various times on subsequent swelling at pH 2.5. Age of tendon in years is indicated for each curve.

the points are widely scattered, but direction of change can be ascertained.

Figure 4 indicates the effect of heating at 56 C. for various times up to one hour on subsequent acid swelling at room temperature. Incubation for one hour caused tendons from all age levels to reach a low range of swelling ability, which is the range of swelling of old tendons previously reported (1). However, the initial rate of loss of swelling ability, as indicated by the change caused by 15-minute heating, showed an inverse proportionality to age. The rate of heat effect, as measured by the decrease in swelling ability on 15 minutes' incubation at 56 C. as a function of age of a large number of tendons, is shown in figure 5. It was not known if the water taken up on heating alone was available for swelling at pH 2.5. Therefore, both original weights and weights after incubation at 56 C. were used for calculation of percentage swelling. Both methods of calculation seemed to yield smooth decay curves of essentially the same shape, beginning in infancy. After the third decade the rate of effect of heat was at a low level and showed only slight decrease with advancing tendon age.

Collagen determinations in control experiments showed that no collagen was extracted during incubation at 56 C. Maintenance of tendon at pH 2.5 for three hours resulted in extraction of about 20% of the hydroxyproline. No significant age difference in amount extracted was noted.

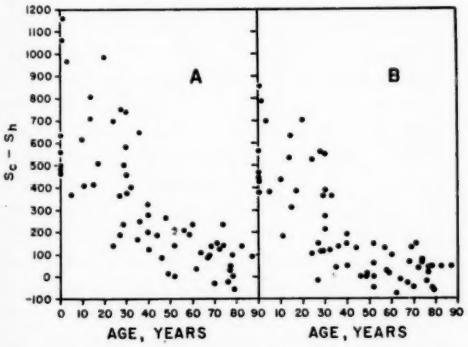

Fig. 5. Effect of incubation at 56 C. for 15 minutes on subsequent acid swelling as a function of age. S_c is percentage swelling of unheated controls; S_h, percentage swelling of heat-treated tendon. For calculation of S_h in graph A, tendon weight after heating was used as initial weight. In graph B, weight before heating was used.

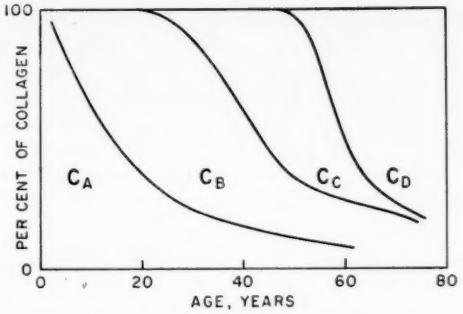

Fig. 6. Proposed amounts of 4 different physical or chemical forms of collagen as functions of age. Amounts represented by areas between curves.

DISCUSSION

The loss of swelling ability with age probably represents changes in the physical or chemical state of the collagen molecule, as there are no significant changes with age in collagen or water concentration of tendon.

The curve for swelling ability versus age in the preceding report (1) indicated that expansible collagen did not decrease significantly until approximately 30 years of age. However, the 15-minute curve of figure 3 and the curves of figure 5 are composed of points which are rates and should indicate values proportional to collagen concentration. These curves show a collagen which decreases steadily from very early life. In addition, the 30-minute curve of figure 3 suggests that a collagen which cannot imbibe water on heating alone develops after around 50 years of age. These curves can be explained on the basis of 4 different physical states of collagen, such that with age the following transformations occur:

$C_A \longrightarrow C_B \longrightarrow C_C \longrightarrow C_D$, where C_A swells in acid, swells without a lag period on heating, and is easily converted by heat to a form which does not swell in acid; C_B swells in acid, swells on heat alone with a lag period, and requires more heat to convert it into a form which will not swell in acid; C_C will not swell in acid but will swell on heating alone with a lag period and C_D will not swell in acid or on heating. The ages during which these forms of collagen would appear are pictured in figure 6. The different forms may represent various stages in unfolding of the collagen molecule with formation of new cross links between polypeptide chains.

In thermal conversion *in vitro* of young tendon, C_B would have to be by-passed as figure 4 shows that young collagen can quickly be converted to non-expansible collagen by heat. Possibly under physiological conditions C_B is stabilized by inorganic ions, by the mechanism by which such ions protect against denaturation of proteins *in vitro* (3).

In order to believe that thermal denaturation at body temperature might cause the changes noted with age in swelling ability of tendon, it would have to be shown that the activation constants of the effects of heat on swelling are such that the conversion of collagen would take around 20 years at 37 C. Attempts were made to determine these constants at elevated temperatures, but the data were not sufficiently accurate to yield a linear Arrhenius plot. Weir (5), using rate of thermal shrinkage of kangaroo tail tendon as a more precise measure of collagen denaturation, found that the reaction appeared first order, and obtained a $\triangle H^*$, the heat of activation, of 141 kcal/mol. Kinetics of the effect of heat on subsequent acid swelling of diaphragm tendon could be determined with reasonable precision at 56 C. Using this rate constant with Weir's value for $\triangle H^*$, the specific reaction rates for thermal conversion of expansible to non-expansible collagen at 37 C. were calculated.

$\triangle H^*$ is within one kcal of being numerically equal to E, the energy of activation. Therefore, Weir's $\triangle H^*$ was substituted for E in the Arrhenius equation,

$$E = \frac{4.575\ T_2\ T_1}{T_2 - T_1} \log \frac{k_2}{k_1}$$

where T_2 and T_1 are 329 K and 310 K, respectively, and k_2 and k_1 are specific reaction rates at these temperatures, k_2 having been experimentally determined. In this way k_1 was calculated. Assuming a first order reaction, k_1 was substituted in the equation,

$$k_1 t = 2.303 \log \frac{Co}{C}$$

where Co is the percentage swelling of untreated tendon, C, the experimentally determined amount of swelling after maximum heat effect, and t, the time required for conversion of Co to C at body temperature.

Values of t for a number of young tendons are shown in table 1. Some of the times are in the appropriate range, while others are too high, but within an order of magnitude of the proper value. Considering the high temperature at which reaction rates were determined, the possibility of alteration of reaction rates under physiological conditions and the fact that minor variation in determination of reaction rates would cause marked variation in t, it is believed these data are consistent with the view that changes in swelling ability of collagen result from thermal denaturation at body temperature.

TABLE 1. CALCULATED TIMES REQUIRED FOR THERMAL CONVERSION OF EXPANSIBLE TO NON-EXPANSIBLE COLLAGEN AT BODY TEMPERATURE.

Tendon Age (Years)	Time Required (Years)
11	53.0
14	8.8
20	72.7
20	13.1
24	54.5
28	108.3
29	17.1
30	58.8

SUMMARY

The relationships of thermal denaturation and age to acid swelling of human diaphragm tendon were investigated. Chemical studies showed that collagen concentration of tendon does not vary significantly with age, suggesting changes in swelling properties are due to transformation of collagen. Heat treatment alone in Ringer's solution causes tendon to increase in weight at a rate and to an extent which are functions of tendon age. Heat treatment also inhibits subsequent acid swelling of tendon at a rate and to an extent which are functions of age. Ability to swell in acid, effect of heat alone, and effect of heat on subsequent acid swelling are different functions of age, necessitating the hypothesis that in aging, collagen passes through four different physical or chemical states. Studies of reaction rates of heat effect on acid swelling yielded data consistent with the view that age changes in swelling ability are due to thermal denaturation at body temperature.

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AGE AND SWELLING IN ACID OF PERIVASCULAR CONNECTIVE TISSUE IN HUMAN LUNG*

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In previous reports (1, 2) it was pointed out that human diaphragm tendon exhibits marked Donnan swelling in acid and alkaline solutions until the third decade, after which there is an abrupt decrease in ability to imbibe water to approximately 50 years of age, with a slower decline in such ability after 50. The changes were most apparent in a pH 2.5 HCl solution. Evidence was presented suggesting the changes with age are due to increasing rigidity of the connective tissue, arising possibly from thermal denaturation of the collagen molecule at body temperature.

Sites where an increasing rigidity of connective tissue with age might be expected to have physiological manifestations are in relation to blood vessels. To discover if perivascular connective tissue shows a decrease in ability to swell with age similar to diaphragm tendon, a histological study of human lung was undertaken.

MATERIALS AND METHODS

Diaphragm tendon was used to find a fixative which would maintain tissues in the swollen state. Tendon fragments were weighed after exposure to a pH 2.5 solution and again after subsequent fixation. A fixative composed of 1 part 40% formalin and 9 parts 0.05 M potassium acid phthalate pH 2.5 buffer was found to give adequate fixation and to preserve most of the swelling which had occurred.

Lung sections were obtained from autopsy cases. Only specimens from individuals over 50 and under 30 years of age were used in order to avoid the period of transformation from expansible to non-expansible collagen which was observed in the case of diaphragm tendon. Undiseased sections from the lingula of the left upper lobe were used. Fragments approximately 1.0 x 0.5 x 0.3 cm. were immersed in 10 to 15 ml. of a pH 2.5 HCl solution for three hours after which they were immersed in the buffered formalin. They were then dehydrated, imbedded in paraffin, sectioned, and stained by Heidenhain's modification of Mallory's aniline blue method.

Eleven specimens between 0 and 30 years of age and 10 between 50 and 87 years of age were treated with acid, sectioned, and stained after fixation in buffered formalin. These specimens were compared with controls, which were not treated with acid. The swelling of the connective tissue of the acid-treated samples was evaluated by another individual as showing slight, moderate, marked, or very marked swelling.

RESULTS

Figure 1 indicates swelling of pulmonary connective tissue in specimens from 10- and 50-year-old individuals. Untreated specimens from young and old have thin connective tissue, while after acid treatment, perivascular and pleural aniline blue positive material is more swollen in the young than in the old specimens.

The results of evaluation of connective tissue swelling in the series of young and old individuals are shown in table 1. There is some overlap in distribution of the extent of swelling. However, swelling of connective tissue at the three sites examined yielded distributions which indicated greater swelling in young than in old. The difference was most apparent in tissue around vessels larger than capillaries and least apparent in the pleura. No connective tissue from the old group showed marked swelling.

DISCUSSION

The findings in this investigation and those from previous studies of diaphragm tendon suggest that transformation of expansible collagen to a rigid form with age may be a generalized process involving all body collagen. Lung was chosen for this study because of its prominent vascular tissue, but there is no reason to believe that perivascular connective tissue from other sites would not show similar change in swelling ability with age. Various physiological mani-

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† U. S. Public Health Service Research Fellow in Pathology.

Fig. 1.
specimen

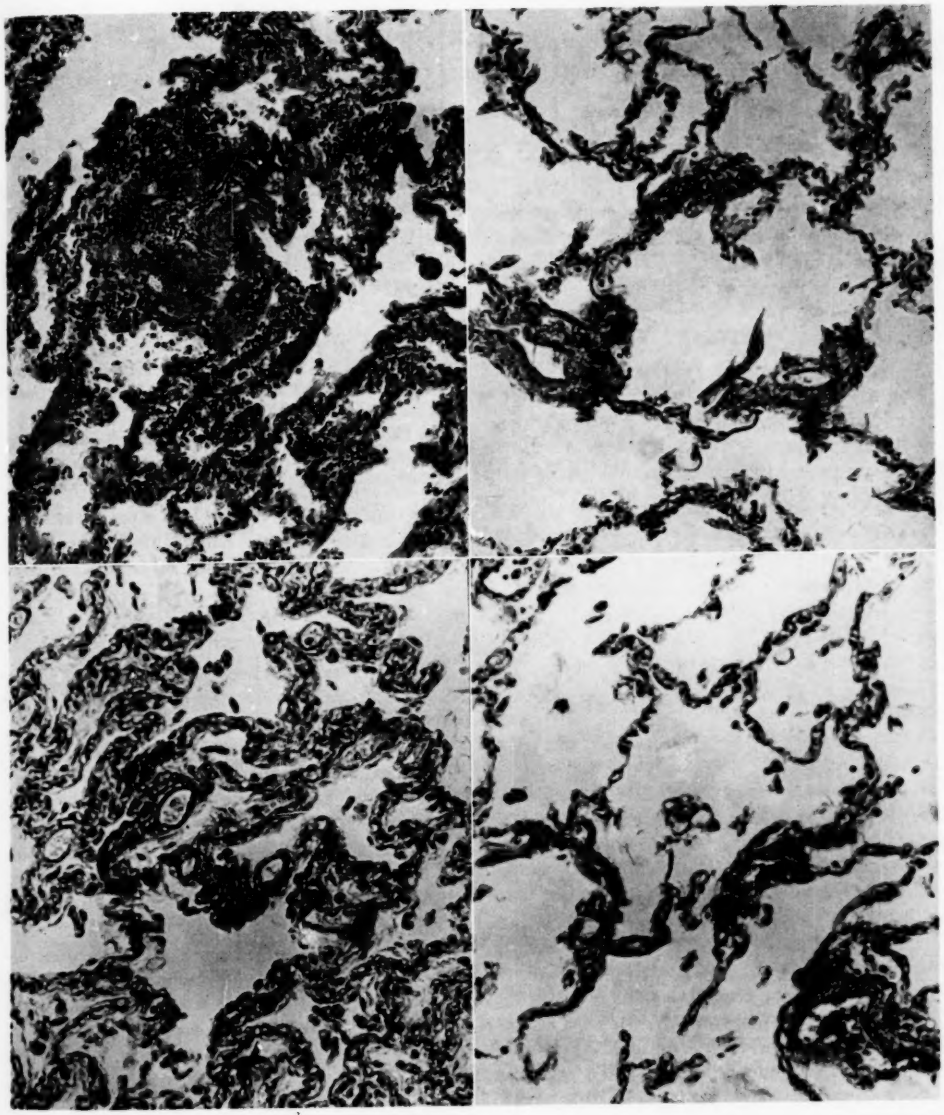

Fig. 1. Sections of lung from 10-year-old individual on left and 50-year-old on right. Bottom, controls; top, specimens exposed to pH 2.5 HCl and fixed in buffered formalin. All stained with Mallory's aniline blue. Magnification 180X. Young specimen shows incidental passive hyperemia.

TABLE 1. NUMBER OF SPECIMENS SHOWING VARIOUS DEGREES OF SWELLING OF COLLAGEN AT THREE SITES.

Specimens	Age	No.	Slight	Moderate	Marked	Very Marked
Pleura	Young	11	1	3	5	2
	Old	10	4	3	3	0
Large vessels	Young	11	1	2	2	6
	Old	10	7	2	1	0
Capillaries	Young	11	2	1	6	2
	Old	10	6	2	2	0

festations of a more rigid perivascular connective tissue can be hypothesized. Restriction of expansion of vessels and inhibition of diffusion of metabolites would be possibilities.

SUMMARY

An histological study of the relationship of age to extent of swelling in acid of connective tissue in human lung was carried out. Connective tissue in pleura and around blood vessels in lungs from young individuals swelled more than that in lungs from aged individuals. The distinction between young and old was most marked in connective tissue around blood vessels larger than capillaries and least marked in pleura.

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VARIATION IN APPEARANCE, CHOLESTEROL CONCENTRATION, AND WEIGHT OF THE CHICKEN AORTA WITH AGE AND SEX

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Although experimental avian atherosclerosis induced by hypercholesterolemia of dietary or hormonal origin is said to resemble the natural disease in both chick and man (16, 19), there are noteworthy differences in histological structure and distribution between spontaneous and experimental lesions of the aorta. The experimental lesion is characterized initially by lipid deposition, mainly in the elastic thoracic aorta, whereas the spontaneous lesion in the chicken is primarily fibrotic and tends to localize in the muscular abdominal aorta. Since the human disease is reportedly more severe in the abdominal aorta (4) and since recent data indicate that the plaques in human and other animals are initally fibrotic with lipid appearing subsequently (2, 18, 19, 21), it would seem that the pattern of development of the spontaneous lesion in the chicken is highly pertinent to the general problem of atherogenesis.

The data most frequently quoted on the development of spontaneous lesions in chickens in relationship to age and sex (11) admittedly suffer from lack of precision regarding age, breed, and previous dietary history; many reports from which normal control values can be extracted deal with limited age brackets or only one sex. Any attempt to compile the results from differentent laboratories is hampered because of possible variations due to season, breed, strain, diet, activity (16, 22, 28, 32) or because of entirely subjective classification. Therefore this study was conducted on both sexes of a wide age-range of genetically similar birds, maintained in a conventional environment on a known diet, and evaluated by techniques which included objective measurements.

MATERIALS AND METHODS

A White Leghorn flock provided 114 genetically similar chickens ranging in age from 5 to 60 months. Four generations were utilized in order to reduce the time interval over which measurements were made. All birds were maintained in enclosed floor pens which provided relative freedom of movement. There were no mechanical temperature or ventilation controls. Their diet during adult life was a standard all-mash laying ration, similar to diet B (31), supplied *ad libitum*. Gross analysis of this feed indicated about 15% protein, 3-4% fat from plant sources (mainly corn and soybean meal), and approximately ½% fat from animal sources (meat scrap). Cholesterol content was estimated as 0.025% by direct analysis of the meat scrap component, using the procedure described below for arterial tissue. Daily feed intake per adult bird under these conditions is generally between 100 and 120 Gm.

Aortic arteriosclerosis was evaluated in three ways: 1) subjective score according to the method of Katz and Stamler (16); 2) cholesterol concentration, mg./Gm. dry tissue (9); and 3) dry weight of aorta in mg./100 Gm. body weight (13). Thoracic and abdominal segments, including 9-12 mm. of each brachiocephalic and 10-12 mm. of each iliac artery, respectively, were processed separately. Certain deviations from described procedures should be noted: scoring ranged from 1.0 for unaffected normal vessels to 6.0 for the most severely affected; dry weight of the cleaned and separated aortic segments was measured after drying for 24 hrs. at 100 C. The cholesterol concentration of the entire dried segment was determined by 1) grinding the segments to a powder in a motorized mortar and pestle, 2) extracting 20-35 mg. of the powder in 5.0 ml. glacial acetic acid for 24 hours., 3) homogenizing the acid extracted material in a glass homogenizer with an additional 5.0 ml of glacial acetic acid, 4) filtering the homogenate through fat-free paper and washing the precipitate with another 5.0 ml. glacial acetic, and 5) carrying 5.0 ml. of the combined filtrate through the procedure of Zlatkis and associates (33) by adding 3.5 ml. of stable color reagent (24) as in plasma cholesterol analysis (31).

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RESULTS

The general appearance of the aortas followed so closely previously documented descriptions (7, 11, 15, 16, 19) that specific details will not be repeated. By 15 months in the male and by 26 months in the female, 100% of the birds showed some gross arteriosclerotic involvement, although a wide range was observed in subjective severity even in the oldest birds. None of the thoracic segments showed the widespread, raised, hardened ridges and plaques encountered in the abdominal aorta.

With regard to the average severity of the condition as graded by gross scoring at 5 months, there was only a slight subjective indication that sclerosis was more severe in the abdominal than in the thoracic segment, and no sex difference was apparent (table 1). With increasing age, the arteriosclerosis score tended to increase for both segments in both sexes, but the difference between thoracic and abdominal became more marked. By 48-60 months, the score suggested that average abdominal involvement was at least 3 times as severe as thoracic. On a sex basis, the female thoracic was at first more affected than the male. After the 26th

TABLE 1. CHANGES IN THE AORTA OF THE CHICKEN WITH AGE.

Sex	Aortic Segment	Atherosclerosis Measurements at Various Ages				
		5 Months	15 Months	26 Months	38 Months	48-60 Months
No. of Birds						
Male		12	12	12	12	4
Female		12	12	12	15	11
Average Body Wt., Gm.						
Male		1925	2229	2411	2482	2002
Female		1341	1687	1770	1747	1588
Subjective Score*						
Male	Thoracic	1.1	1.2	1.2	1.3	1.5
	Abdominal	1.2	1.9	3.0	3.2	4.8
Female	Thoracic	1.1	1.2	1.4	1.4	1.4
	Abdominal	1.2	1.5	2.5	2.6	3.5
Pooled Standard Error		0.02	0.08	0.16	0.81	0.34
Cholesterol, mg./Gm. Dry Weight of Vessel						
Male	Thoracic	10.7	12.0	12.5	13.7	16.2
	Abdominal	10.2	13.0	14.4	21.9	34.5
Female	Thoracic	13.0	19.3	23.4	27.0	26.1
	Abdominal	11.6	14.1	20.8	25.6	37.7
Pooled Standard Error		0.44	1.38	1.15	2.28	5.85
Dry Weight of Vessel, mg./100 Gm. Body Weight						
Male	Thoracic	5.2	6.0	6.2	5.2	(6.0)†
	Abdominal	1.4	4.1	4.8	5.5	(6.2)
Female	Thoracic	3.7	4.5	4.6	4.6	(4.6)
	Abdominal	0.9	1.8	2.6	3.5	(4.8)
Pooled Standard Error		0.10	0.21	0.24	0.26	....

* Score ranged from 1.0 for normal to 6.0 for most severely affected vessels.
† Bracketed values were estimated from extrapolated curves.

month, however, the female condition apparently stabilized, while that of the male intensified until it equalled that of the female. On the other hand, male abdominal sclerosis as estimated grossly, was considerably more severe than that of the female abdominal segment over the whole age span.

There was little difference between segments within a sex or between sexes with regard to cholesterol concentration at 5 months (table 1). In the male, both segments show increased deposition with age, but the abdominal increments are proportionally greater. By the 38th month the cholesterol level of the male abdominal segment is significantly higher than the thoracic, and by 48-60 months is twice as high. Cholesterol concentration of both the female segments increases more rapidly with age than the male. Through the 38th month it is the thoracic which has the higher content, but thereafter the thoracic level apparently stabilizes, while the abdominal concentration continues to rise. Both segments of the female aorta contain higher cholesterol levels than their male counterparts throughout the age span, but the difference is less marked between abdominal segments. Cholesterol concentrations as high as 70 mg./Gm. dry aortic tissue were encountered in a few abdominal segments of both sexes.

Structural differences between thoracic and abdominal segments (11), and expected differences in vessel diameters and wall thickness between males and females due to a sex difference in blood pressure (6, 26) probably limit use of aortic weight measurements to changes with age within a segment. These restrictions are illustrated in the 5-month data, which show that the thoracic segment of the aorta of either sex weighed approximately 4 times the abdominal portion, and the weights of the male segments were about 1½ times greater than their female counterparts. Nevertheless, weight changes with age within a segment apparently reflected to some degree the fibrotic proliferation seen grossly. For the thoracic aortic segments of either sex, a comparatively small weight increment occurred between 5 and 15 months, but thereafter either stabilized or actually decreased. On the other hand, the weight of the abdominal segments increased continuously with age, reaching values in the oldest birds that were 4-5 times that of the youngest. (Because of a technical error, segment weights were not obtained for the oldest age groups but were estimated from extrapolated curves drawn in conformity with the existing data).

The essentially parallel trends among score, cholesterol concentration, and weight of the dry aorta suggest that any one of these measurements would have estimated the major arteriosclerotic changes with age. In some cases, however, interpretation of relative sclerotic severity would have differed if only one of the measurements had been used. For example, arteriosclerosis of the older female thoracic segments would grade almost twice as severe, based only on the rise in cholesterol concentration, than is supported by either the increase in score or of weight. Conversely, cholesterol levels would tend to underestimate male abdominal arteriosclerosis, and score alone, at least as used in our hands, would have underestimated female abdominal severity.

It seemed reasonable, therefore, that a combination of these three measurements would be a more reliable index of arteriosclerosis. A value of 1 was arbitrarily assigned to each measurement for each segment of each sex at 5 months of age. This should not bias the results since differences at this age were small and atherosclerosis minimal. All subsequent measurements were then expressed relative to the 5-month value, averaged, and labeled "sclerotic severity." Since the range of changes which each parameter underwent with age was approximately the same, each contributed nearly equally to the index.

A plot of sclerotic severity vs. age is presented in figure 1. The much greater sclerotic involvement of the abdominal aorta over the thoracic is clearly shown, for both male and female, as well as the slightly more severe condition in the male abdominal than in the female abdominal segment. The female thoracic aorta tends to be more involved than in the male's over most of the age range studied, but after 38 months the female condition tends to stabilize while that of the male intensifies. Finally the much more pronounced increase in sclerotic severity with age in the abdominal compared to the thoracic portion is readily observed.

DISCUSSION

As the curves for relative sclerotic severity suggest (fig. 1), spontaneous abdominal arteriosclerosis is not only 4 times as severe by the 4th-5th year as at 5 months, but shows all indica-

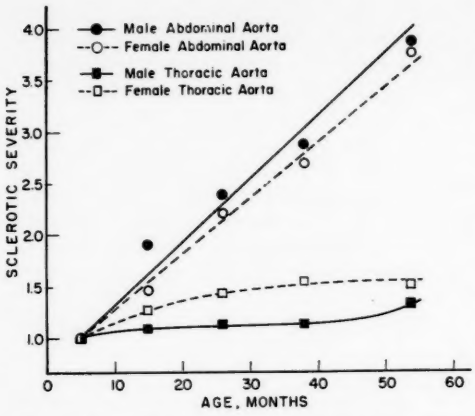

Fig. 1. Change in relative severity of aortic atherosclerosis with age in the chicken, computed from the gross score, cholesterol concentration, and dry weight of vessel.

tions of further intensification with age. These data extend observations on males raised for 1-2 years on diets without added fat (15, 19) and demonstrate that progressively more severe lesions develop with increasing age in both sexes of the chicken in the absence of what might be termed "atherogenic" quantities of dietary cholesterol. The estimated 0.025% cholesterol in the ration is well below the 0.25% used to produce experimental lesions with minimal organ lipidosis (25), and even below the 0.1% minimum required before any organ accumulation is detected (10). Simple reduction of dietary cholesterol will apparently neither prevent the natural disease nor even halt its progressive increase in severity, particularly as it appears in the abdominal aorta of the chicken. Similar conclusions may apply to the human, if in fact the lesions of the muscular aorta of the bird are typical of the disease seen in man (15, 18, 19).

This study of the development of spontaneus avian arteriosclerosis through a longer age span and under more controlled conditions than heretofore, serves to re-emphasize some of the evidence linking the lesions of the abdominal aorta of the chicken with the human disease, and perhaps even for questioning the relationship of the induced thoracic lesion to the naturally occurring disease. Thus, somewhat as in the human (4), the predilection of spontaneous atheroma for the abdominal aorta of the chicken becomes more pronounced as the bird ages. This is essentially opposite of the distribution of lesions reported for the experimental disease in cockerels (16).

The biochemical measurements show, too, that cholesterol normally appears in increasing concentrations in the atheromatous areas of the aorta of the male chicken, reaching levels which are as high as those found in many cases of experimental atherosclerosis (9, 16, 17, 20). In time, then, the spontaneous abdominal lesions take on the characteristics considered typical of atheroma. Histochemical observations which have indicated that cholesterol is rare or present only in small amounts in such lesions (7, 16, 19) were generally based on material under 2 years of age. The apparent lag of cholesterol accumulation behind tissue proliferation in the spontaneous lesion of the male chicken seems to fit the pattern currently described for arteriosclerosis in other animals, including humans (2, 18, 19, 21). Again, as with the gross lesions, the distribution of cholesterol along the aorta of the older arteriosclerotic male chickens is opposite to that found in the experimental disease in cockerels (28).

On the other hand it was somewhat surprising that, even after 4-5 years of cholesterol being deposited in high or increasing concentration in the thoracic aorta, the vessel walls of this segment showed so little gross thickening and fibrotic proliferation in comparison to the abdominal aorta. It is the fibrotic changes which appear secondary to lipid in the cholesterol and estrogen induced condition which seem to have been the basis for considering the experimental disease as typical of both spontaneous avian and human atherosclerosis (16). Perhaps apropos here are the comments of Blumenthal (1) and Paterson (23) that in well developed cases of human arteriosclerosis, the fibrotic component frequently exceeds the lipid content of the lessions which encroach upon the lumen of the vessel.

In an attempt to compare the aortic cholesterol levels with those of the human, consideration was given to the fact that the intima and media of the chicken aorta were analyzed together and that the chicken apparently ages 10 times as fast as man, since its maximum expected life span seems to be between 8 and 10 years (8, 14). Thus our thoracic segment cholesterol values of 16-26 mg./Gm. at 4-5 years may be contrasted with human thoracic levels of 63 mg./Gm. between 40 and 49 years (12).

The increase of 3 mg./Gm. in the rooster's thoracic level between 5 and 38 months, when fibrosis and cholesterol sequestration seemed to be minimal, may also be compared to the increase of 8 mg./Gm. between 5 and 30 years in human aortas with minimal atherosclerosis (5, chart I). For sclerotic vessels, descriptive evidence indicates that abdominal atherosclerosis of 4- to 5-year-old chickens approximates grade 2 (at mean age, 64 yrs.) in the human (5). Corresponding cholesterol concentrations are 34-38 and 95 mg./Gm. for chicken and human, respectively. (Wet weight values were multiplied by 4 to convert to a dry weight basis) (12).

These comparisons suggest that normal and sclerotic areas of the chicken aorta concentrate cholesterol about ⅓ the rate of corresponding human aortas, on a relative age basis, but about 3 times as fast per unit of elapsed time. The chicken aortic cholesterol values are, however, anywhere from 3 to 6 times greater than in the untreated young or middle-age rabbit, a species also widely used in atherosclerotic studies (29).

The slightly greater severity of male abdominal arteriosclerosis over the female indicates that a sex factor may be operative, but that it produces nowhere near the 9:1 male:female incidence ratio reported in wild fowl (16). The comparatively small sex difference found in the present study agrees with Dauber's data (11). The explanation for the greater severity of the rooster's lesions in the presence of a generally lower plasma cholesterol (30) lies perhaps in the higher blood pressure of the adult male (26), in accordance with hemodynamic theories on atherogenesis (3, 27). These results suggest that the hen and rooster should be equally suitable for the study of spontaneous arteriosclerosis of the abdominal aorta.

SUMMARY

The development of spontaneous aortic arteriosclerosis was studied in 4 generations of a standard-fed, uniformly-treated, genetically similar group of 114 White Leghorns ranging up to 5 years of age. Progressively more severe arteriosclerosis, as measured by score, cholesterol concentration, and aortic weight increment, developed in both males and females, although the diet can be considered non-atherogenic, i.e., contained approximately 0.025% cholesterol and 4-5% fat.

The abdominal aorta was progressively more afflicted than the thoracic, attaining on a comparative basis a 4-fold difference in the oldest birds. The male abdominal was only slightly more affected than the female. Cholesterol concentration increased progressively in the atheromatous segments, but in the male at least at a slower rate than the fibrotic proliferation. For the 4 to 5-year-old birds, average concentrations were 34 mg./Gm. in the abdominal and 16 mg./Gm. in the thoracic of the male, and 38 and 26 mg./Gm. for the female. This distribution of lesions and of cholesterol along the aorta is reverse of that reported following cholesterol feedings or estrogen administration in cockerels. The elevated levels of cholesterol impart to the spontaneous lesions of the abdominal aorta the characteristics typical of atheroma, whereas despite high or increasing levels of cholesterol comparatively little gross fibrotic proliferation develops in the thoracic aorta.

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THE GLUCOSE-6-PHOSPHATE AND 6-PHOSPHOGLUCONATE DEHYDROGENASE ACTIVITIES OF ARTERIAL TISSUE IN INDIVIDUALS OF VARIOUS AGES*

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The present study was undertaken with the purpose of determining the glucose-6-phosphate dehydrogenase (G-6-PDH) and 6-phosphogluconate dehydrogenase (6-PGDH) activities of the aorta, pulmonary artery and coronary artery in individuals of various ages. In the case of the aortic and coronary artery samples the enzyme measurements were carried out both on apparently normal tissue portions and on arterial segments which were the site of arteriosclerotic changes.

MATERIALS AND METHODS

Eighty-five samples of the human aorta (thoracic descending), 78 samples of the pulmonary artery, and 45 samples of the coronary artery were obtained fresh at autopsy at the St. Louis City Morgue.† Aqueous homogenates (2.5 and 5.0%) of intima-media segments of the arteries were prepared as described in previous publications (3, 5).

The activities of the G-6-PDH and 6-PGDH were measured in separate experiments through determination of the quantities of TPNH formed in the reactions. The temperature of incubation was 38 C.; readings were made at 340 mμ in a Beckman DU spectrophotometer at 0, 30, and 60 minutes.

The final millimolar substrate-buffer concentrations used in the G-6-PDH tests (total volume, 3.0 ml.) were: glucose-6-phosphate sodium (Sigma), 5.5; TPN, 1.4; 2-amino-2-methyl-1-propanol, 100; ethylenediamine tetraacetic acid, 1; tris(hydroxymethyl)aminomethane, 0.67; nicotinamide, 2.4; magnesium chloride, 10. The pH of the buffer-substrate mixture was 8.8. An amount of homogenate corresponding to 25 mg. of fresh tissue was employed in each test. A blank containing the same quantities of tissue and buffer substrate, but without the addition of TPN, was run with each sample.

In the 6-PGDH experiments the final millimolar concentrations (total volume, 3.0 ml.) were: 6-phosphogluconate potassium (prepared from 6-phosphogluconate barium, Sigma), 1.67; TPN, 1.4; 2-amino-2-methyl-1-propanol, 100; ethylenediamine tetraacetic acid, 1; nicotinamide, 2.4; potassium chloride, 10; magnesium chloride, 10. The pH of the buffer-substrate mixture was 8.8. An amount of homogenate corresponding to 50 mg. of fresh tissue was employed in each test. A blank containing the same quantities of tissue and buffer-substrate, but without the addition of TPN, was run with each sample.

A high degree of proportionality was found between time of incubation and recorded enzyme activities in both the G-6-PDH and 6-PGDH determinations over the 60-minute experimental period used. Proportionality was further observed between the quantities of tissue employed and the measured activities over a 5-25 mg. range in the G-6-PDH experiments (5-50 mg. range for a 30-minute incubation period) and a 10-75 mg. range in the 6-PGDH determinations. In evaluation of the recorded data it should be noted that under the conditions of the G-6-PDH experiments the amount of TPNH formed is the result not only of the oxidation of the added substrate (glucose-6-phosphate) by the G-6-PDH, but also of the oxidation of the formed product (6-phosphogluconate) by the 6-PGDH. Because the activity of the latter enzyme is rather low in aortic and pulmonary artery tissue the correction of the recorded G-6-PDH activity values for the concomitant 6-PGDH activity would be small.

Determinations of tissue nitrogen and cholesterol contents were performed as described previously (3).

RESULTS

Aortic Samples

I. Normal Aortic Tissue

Glucose-6-Phosphate Dehydrogenase—It will be seen from the data recorded in table 1 that

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† The authors are indebted to Dr. J. J. Connor for assistance in obtaining specimens.

TABLE 1. GLUCOSE-6-PHOSPHATE AND 6-PHOSPHOGLUCONATE DEHYDROGENASE ACTIVITIES OF 85 HUMAN AORTIC SAMPLES AND 78 PULMONARY ARTERY SAMPLES.

No.	Age (Years)	Sex, Race	Normal Aortic Tissue					Arteriosclerotic Aortic Tissue					Pulmonary Artery Tissue				
			Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N / Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour
1	0.03	MC	0.1	0.023	0.58	0.012	0.30										
2	0.12	MW	0.1	0.026	0.56	0.008	0.20										
3	0.15	MW	0.4	0.038	0.94	0.034	0.85						0.5	0.014	0.37	0.022	0.58
4	0.15	MC	0.1	0.025	0.71	0.018	0.51						0.1	0.013	0.35	0.010	0.27
5	0.25	MW	0.1	0.014	0.35	0.005	0.13						0.1	0.014	0.22	0.006	0.10
6	0.40	FW	0.1	0.018	0.43	0.008	0.20						0.1	0.028	0.69	0.012	0.31
7	0.40	FC	0.3	0.056	1.25	0.018	0.41						0.2	0.037	0.78	0.016	0.35
8	0.85	FW	0.1	0.040	1.25	0.006	0.18										
9	1	FW	0.1	0.027	0 62	0.020	0.46						0.1	0.027	0.70	0.013	0.33
10	1.5	MC	0.4	0.056	1.27								0.5	0.062	1.72		
11	2	FW	0.1	0.027	0 60	0.014	0.31						0.1	0.029	1.04	0.006	0.22
12	3	MW		0.131	3.81												
13	3.5	MW	0.2	0.026	0.59	0.008	0.19						0.1	0.018	0.43	0.002	0.05
14	5	FC	0.1	0.024	0.56	0.010	0.23						0.2	0.035	0.91	0.008	0.21
	Mean...		0.2	0.038	0.97	0.013	0.33						0.2	0.028	0.72	0.011	0.27
15	16	MW	0.2	0.068	1.79	0.007	0.18						0.2	0.148	3.88	0.015	0.40
16	17	FW	0.4	0.095	2.08	0.012	0.25						0.3	0.082	2.01	0.025	0.62
17	18	MW	0.3	0.144	6.75	0.012	0.53						0.3	0.107	2.75	0.015	0.39
18	19	MW	0.3	0.110	2.65	0.016	0.38	0.8	0.114	2.62	0.010	0.23	0.3	0.114	3.01	0.021	0.55
	Mean...		0.3	0.104	3.32	0.012	0.34	0.8	0.114	2.62	0.010	0.23	0.3	0.113	2.92	0.019	0.49
19	28	MW	0.3	0.112	2.95	0.011	0.28	0.6	0.128	3.70	0.010	0.29	0.2	0.116	3.18	0.012	0.33
20	28	FC	0.6	0.110	2.94	0.013	0.35						0.2	0.089	2.41	0.014	0.38
	Mean...		0.5	0.111	2.95	0.012	0.32	0.6	0.128	3.70	0.010	0.29	0.2	0.103	2.80	0.013	0.36
21	30	FC	0.5	0.122	3.29			0.8	0.080	2.08			0.3	0.073	2.33		
22	31	MW	0.6	0.339	9.48			2.0	0.080	2.31							
23	31	MW	0.2	0.049	1.22	0.016	0.40						0.2	0.068	1.42	0.010	0.20
24	31	FW	0.3	0.118	2.38								0.3	0.121	3.44		
25	32	MC	0.4	0.167	3.90	0.009	0.21	0.4	0.076	1.68	0.007	0.16	0.2	0.049	1.25	0.008	0.21
26	33	MC	0.5	0.104	2.45	0.008	0.20						0.2	0.093	2.52	0.018	0.49
27	34	FW	0.5	0.064	1.46	0.005	0.11						0.1	0.117	3.22	0.025	0.68
28	34	FW	0.7	0.054	1.31								0.5	0.133	3.60		
29	36	FW	0.2	0.109	2.78	0.009	0.22	0.2	0.078	1.97	0.009	0.21	0.1	0.057	1.76	0.015	0.46
30	37	FC	0.6	0.053	1.59	0.007	0.22	1.0	0.053	1.33	0.008	0.21	0.3	0.039	1.00	0.004	0.10
31	38	FW	0.3	0.123	3.14	0.005	0.14	0.4	0.063	1.59	0.007	0.19	0.2	0.052	1.41	0.013	0.36
	Mean...		0.4	0.118	3.00	0.009	0.22	0.8	0.061	1.82	0.008	0.19	0.2	0.080	2.20	0.013	0.36
32	43	MW	0.6	0.124	2.94			0.5	0.100	2.45			0.2	0.083	2.11		
33	43	MW		0.202	6.54	0.013	0.43		0.165	7.36	0.014	0.62		0.156	4.35	0.015	0.43
34	43	FC	0.2	0.080	2.73	0.013	0.44	0.2	0.077	1.84	0.009	0.22	0.3	0.049	1.56	0.006	0.19
35	44	MW	2.2	0.166	4.72	0.017	0.49	2.1	0.074	2.60	0.027	0.96	0.4	0.084	2.17	0.019	0.50
36	44	MC	0.2	0.127	3.49	0.012	0.32	1.2	0.080	2.25	0.007	0.20	0.2	0.089	3.16	0.015	0.53
37	45	MW	0.3	0.107	3.00	0.011	0.32	0.8	0.091	2.47	0.012	0.32	0.3	0.098	2.56	0.019	0.51
38	46	MW	0.2	0.113	2.90	0.012	0.30						0.4	0.125	3.38	0.026	0.69
39	46	MW	0.5	0.133	3.52	0.009	0.25	1.1	0.063	1.56	0.015	0.37	0.2	0.058	1.67	0.010	0.27
40	47	MW	0.4	0.133	3.95	0.008	0.22	5.3	0.041	1.26	0.017	0.54	0.6	0.115	2.90	0.020	0.51
41	47	MW	0.4	0.080	1.89	0.007	0.17	0.7	0.049	1.29	0.011	0.29	0.2	0.027	0.91	0.015	0.51
	Mean...		0.6	0.127	3.57	0.011	0.33	1.5	0.082	2.56	0.014	0.44	0.3	0.088	2.48	0.016	0.46
42	50	MW	0.4	0.106	2.88	0.010	0.27	0.7	0.044	1.18	0.011	0.30	0.3	0.052	1.48	0.014	0.38
43	50	MW	0.5	0.089	2.75	0.017	0.53	1.3	0.070	2.21	0.026	0.80	0.2	0.035	1.11	0.007	0.24
44	50	FW	0.4	0.069	1.68	0.004	0.10	1.1	0.066	1.68	0.008	0.20	0.2	0.055	1.44	0.013	0.34
45	50	FC		0.081	2.18	0.015	0.40	2.2	0.035	1.21	0.009	0.31		0.042	1.45	0.013	0.43
46	52	MW	0.8	0.100	3.19	0.013	0.42	2.8	0.067	2.53	0.011	0.40	0.3	0.094	3.09	0.024	0.79

TABLE 1. (Continued)

No.	Age (Years)	Sex, Race	Normal Aortic Tissue					Arteriosclerotic Aortic Tissue					Pulmonary Artery Tissue				
			Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour
47	52	MW	0.7	0.070	2.10	0.010	0.29	1.6	0.081	2.65	0.011	0.37	0.4	0.081	2.30	0.022	0.61
48	52	MW	0.6	0.066	1.82	0.006	0.16	1.0	0.045	1.37	0.007	0.21	0.4	0.077	2.64	0.022	0.76
49	52	MW	0.3	0.069	1.82	0.013	0.34	0.5	0.067	2.09	0.008	0.24	0.4	0.102	2.82	0.011	0.30
50	52	FW	0.6	0.051	1.38	0.010	0.27						0.4	0.033	0.97	0.014	0.39
51	53	MW	0.9	0.086	2.51	0.017	0.49	1.8	0.083	2.17	0.010	0.26	1.1	0.106	2.61	0.019	0.47
52	53	MW	0.5	0.182	5.25	0.015	0.44	1.5	0.076	2.08	0.012	0.33	0.6	0.064	1.86	0.018	0.52
53	54	MW	0.8	0.240	7.61			5.0	0.050	1.43			0.3	0.154	6.60		
54	54	MW	1.2	0.194	5.80	0.016	0.46	3.2	0.086	2.70	0.019	0.62	0.3	0.109	2.92	0.019	0.50
55	56	MW		0.220	5.38				0.174	4.42				0.113	3.13		
56	57	MW	1.0	0.113	3.13	0.012	0.32	2.2	0.074	2.48	0.010	0.34	0.9	0.113	2.98	0.009	0.24
57	57	MW	0.5	0.023	0.64	0.007	0.18	0.7	0.030	0.75	0.007	0.18	0.2	0.053	1.51	0.012	0.35
58	58	MW						2.2	0.110	4.87	0.009	0.41	0.5	0.029	1.19	0.012	0.49
59	58	MW	0.5	0.086	2.27	0.014	0.36	1.1	0.031	0.84	0.005	0.13	0.2	0.040	1.26	0.015	0.49
60	59	MW	0.8	0.086	2.64	0.007	0.23	4.1	0.035	1.06	0.004	0.12	0.6	0.104	3.88	0.019	0.70
61	59	MW	0.6	0.033	0.85	0.011	0.32	1.3	0.027	0.74	0.007	0.19					
62	59	FW	1.3	0.094	2.25	0.009	0.22	2.2	0.042	1.23	0.009	0.26	0.5	0.056	1.54	0.011	0.31
		Mean...	0.7	0.103	2.91	0.011	0.29	1.9	0.065	1.98	0.010	0.31	0.4	0.076	2.34	0.015	0.46
63	60	MW	0.7	0.029	0.97	0.017	0.57	1.3	0.038	1.19	0.004	0.14	0.3	0.043	1.29	0.016	0.49
64	61	FW	0.7	0.096	2.96	0.012	0.36	1.1	0.119	3.86	0.008	0.27	0.1	0.070	2.47	0.005	0.16
65	62	MW	0.3	0.033	0.87	0.004	0.12	0.7	0.014	0.36	0.010	0.27	0.4	0.058	1.54	0.019	0.51
66	62	FW	0.6	0.094	2.84	0.011	0.35	1.1	0.054	1.54	0.006	0.17	0.4	0.068	2.15	0.019	0.58
67	62	FW	0.9	0.178	5.41			1.6	0.090	5.19			0.5	0.113	2.76		
68	63	MW	0.4	0.099	2.80	0.008	0.23	0.4	0.090	1.28	0.007	0.09	0.4	0.130	3.21	0.021	0.53
69	63	MW	0.5	0.121	3.23	0.023	0.63	1.2	0.070	1.92	0.005	0.13	0.2	0.053	1.67	0.013	0.40
70	63	MW	0.8	0.068	2.04	0.010	0.30	1.9	0.073	2.00	0.004	0.12	0.3	0.091	2.95	0.010	0.32
71	63	MC	1.3	0.195	4.18			1.1	0.087	2.84			0.6	0.066	2.20		
72	64	MW	0.9	0.055	1.48								0.9	0.045	1.18		
73	64	MW	0.7	0.213	6.63			3.0	0.123	4.76			0.6	0.181	6.21		
74	65	MW	0.7	0.018	0.71			5.5	0.003	0.10			0.5	0.017	0.54		
75	65	MW	0.7	0.039	1.10	0.004	0.12	2.1	0.033	0.99	0.007	0.20	0.9	0.047	1.29	0.005	0.13
76	65	MW	0.6	0.110	3.02	0.004	0.12	0.8	0.079	1.95	0.008	0.20	0.2	0.056	1.54	0.010	0.27
77	67	MW	1.0	0.077	1.97			3.8	0.031	0.78			0.7	0.034	0.91		
78	67	MW	1.1	0.169	4.44			3.2	0.105	3.65				0.158	3.87		
79	67	MW						2.4	0.065	2.45	0.013	0.50	0.4	0.080	2.23	0.016	0.45
80	68	MW	0.5	0.099	2.61	0.012	0.32	2.0	0.055	1.85	0.008	0.29	0.4	0.118	3.42	0.014	0.42
81	69	MW	0.8	0.147	2.69			1.7	0.061	1.86			0.3	0.112	3.12		
		Mean...	0.7	0.102	2.78	0.011	0.31	1.9	0.066	2.14	0.007	0.22	0.5	0.081	2.35	0.014	0.39
82	72	MW		0.067	2.62	0.010	0.41							0.021	0.60	0.021	0.58
83	73	FW	0.6	0.107	2.83	0.008	0.20	1.5	0.060	1.84	0.004	0.14	0.3	0.060	1.96	0.011	0.35
84	75	FW	0.8	0.133	3.96	0.014	0.42	4.9	0.054	2.45	0.014	0.64					
		Mean...	0.7	0.102	3.14	0.011	0.35	3.2	0.057	2.15	0.009	0.39	0.3	0.041	1.28	0.016	0.47
85	85	MC	0.6	0.070	2.16	0.009	0.27	1.0	0.056	1.68	0.007	0.21	0.4	0.072	2.26	0.010	0.31
		Mean...	0.6	0.070	2.16	0.009	0.27	1.0	0.056	1.68	0.007	0.21	0.4	0.072	2.26	0.010	0.31
Grand Mean*...			0.6	0.108	3.00	0.011	0.31	1.7	0.070	2.15	0.010	0.30	0.4	0.081	2.36	0.015	0.43

* Excluding 0-5 year group.

the G-6-PDH activity of samples obtained from children aged 0-5 years in general was found to be considerably lower than the activity of samples from adults. Thus the average quantity of glucose-6-phosphate metabolized by samples from children was 0.038 mM/Gm. wet tissue/hour, and 0.97 mM/Gm. tissue nitrogen/hour, as compared with mean activity values of 0.108 mM/Gm. wet tissue/hour and 3.00 mM/Gm. tissue nitrogen/hour for non-arteriosclerotic samples from individuals aged 16-85 years. No significant variation in enzyme

TABLE 2. COEFFICIENTS OF CORRELATION BETWEEN AGE AND ENZYME ACTIVITIES FOR SAMPLES FROM INDIVIDUALS AGED 16-85 YEARS.

	Wet Tissue			Tissue Nitrogen		
	r	N	t	r	N	t
Aorta						
G-6-PDH	−0.12	69	0.10	−0.10	69	0.08
6-PGDH	−0.04	54	0.03	+0.04	54	0.03
Pulmonary Artery						
G-6-PDH	−0.20	68	0.17	−0.10	68	0.08
6-PGDH	−0.16	54	0.12	−0.05	54	0.04
Coronary Artery						
G-6-PDH	+0.26	28	1.38	+0.26	23	1.24
6-PGDH	−0.01	28	0.05	+0.08	23	0.37

activity with age was observed for the samples from the latter group (table 2).

The G-6-PDH activity of the samples derived from women was 88% of that found for men when expressed on the basis of wet tissue weight, and 66% when calculated on the basis of the tissue nitrogen content.

6-Phosphogluconate Dehydrogenase—The average quantity of 6-phosphogluconate metabolized by the normal aortic tissue (table 1) was 0.013 mM/Gm. wet tissue/hour for the samples obtained from children, and 0.011 mM for the samples from adults. The corresponding values, expressed on the basis of tissue nitrogen content, were 0.33 and 0.31 mM. No significant change in enzyme activity with age was noted (table 2). The 6-PGDH activity of the samples obtained from women was 89% of that found for men, when calculated on the basis of wet tissue weight, and 85%, when expressed on the basis of tissue nitrogen content.

II. Arteriosclerotic Aortic Tissue

Enzyme activity measurements were performed on 58 samples of arteriosclerotic aortic tissue; in 56 of these samples sufficient normal tissue was available to permit determinations also on the normal portions of the vessel wall.

In table 3 the average enzyme values of arteriosclerotic samples have been recorded for various age groups in percentages of the values found for normal tissue. It will be seen from the table that significantly lower G-6-PDH values were observed for the arteriosclerotic tissue in all the age groups included in the table. In contrast to this, the average 6-PGDH values of the arteriosclerotic tissue were found to be higher than the values for the normal tissue for the age groups 30-39 and 40-49 years; the t values of the differences were, however, not statistically significant. For the older age groups, 50-59 and 60-75 years, the mean 6-PGDH activities of the arteriosclerotic tissue were found to be slightly lower than those of the normal aortic tissue.

Pulmonary Artery Samples

Glucose-6-Phosphate Dehydrogenase—In accordance with the observations on normal aortic tissue the average G-6-PDH activity of pulmonary artery samples (table 1) obtained from children aged 0-5 years was found to be markedly lower (0.028 mM glucose-6-phosphate metab./Gm. wet tissue/hour; 0.72 mM/Gm. tissue nitrogen/hour) than the values recorded for samples from adults (0.081 mM/Gm. wet tissue/hour; 2.36 mM/Gm. tissue nitrogen/hour). No significant change in enzyme activity with age was found for the 16-85 year group (table 2). The mean values observed for the

TABLE 3. MEAN ENZYME ACTIVITIES OF ARTERIOSCLEROTIC TISSUE EXPRESSED IN PERCENTAGES OF ACTIVITIES OF NORMAL TISSUE OF THE SAME AORTIC SAMPLES.

Age Group (Years)	G-6-PDH					6-PGDH				
	Wet Tissue			Tissue Nitrogen		Wet Tissue			Tissue Nitrogen	
	N	%	t of diff.	%	t of diff.	N	%	t of diff.	%	t of diff.
30-39	6	60	2.10	56	2.13	4	108	0.29	101	0.24
40-49	9	65	4.00	68	2.79	8	126	1.43	139	1.38
50-59	19	68	3.78	72	3.18	17	94	1.24	99	1.80
60-75	19	65	4.82	71	4.80	12	94	2.21	94	1.42

TABLE 4. GLUCOSE-6-PHOSPHATE AND 6-PHOSPHOGLUCONATE DEHYDROGENASE ACTIVITIES OF 45 CORONARY ARTERY SAMPLES.

			Normal Coronary Artery Tissue					Arteriosclerotic Coronary Artery Tissue				
No.	Age (Years)	Sex, Race	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour
14	5	FC	0.1	0.037	0.95	0.016	0.40					
	Mean		0.1	0.037	0.95	0.016	0.40					
15	16	MW	0.1	0.068	1.48	0.020	0.44					
16	17	FW	0.4	0.036		0.007						
	Mean		0.3	0.052	1.48	0.014	0.44					
19	28	MW	0.1	0.135	4.46	0.016	0.55	0.4	0.134	4.65	0.025	0.88
20	28	FC	0.1	0.114	3.41	0.036	1.10					
	Mean		0.1	0.125	3.94	0.026	0.83	0.4	0.134	4.65	0.025	0.88
23	31	MW	0.2	0.091	2.92	0.026	0.83	0.2	0.089	2.79	0.024	0.76
25	32	MC	0.2	0.093	2.76	0.012	0.36					
27	34	FW	0.2	0.072	2.78	0.013	0.49					
29	36	FW	0.1	0.083	2.39	0.015	0.45					
30	37	FC	0.3	0.072	1.93	0.025	0.67					
31	38	FW	0.1	0.056	1.47	0.008	0.21					
	Mean		0.2	0.077	2.38	0.017	0.50	0.2	0.089	2.79	0.024	0.76
34	43	FC	0.1	0.051	1.57	0.023	0.70					
35	44	MW	0.6	0.044	1.07	0.030	0.73	4.2	0.069		0.024	
36	44	MW	0.1	0.141	4.72	0.024	0.81	2.3	0.088	3.62	0.017	0.71
37	45	MW	0.8	0.082	2.17	0.017	0.46	4.4	0.057	2.53	0.018	0.78
39	46	MW						1.7	0.076	2.52	0.029	0.95
40	47	MW	1.5	0.069		0.028		2.2	0.052	1.47	0.019	0.53
41	47	MW	0.2	0.116	3.59	0.039	1.20	0.3	0.049	1.41	0.024	0.68
	Mean		0.6	0.084	2.62	0.027	0.78	2.5	0.065	2.31	0.022	0.61
42	50	MW		0.067	2.12	0.035	1.12	1.8	0.044	1.43	0.020	0.66
43	50	MW						2.3	0.149	5.18	0.018	0.63
44	50	FW						2.9	0.068	2.16	0.014	0.46
47	52	MW	1.3	0.105	2.82	0.020	0.53	3.1	0.079	2.43	0.017	0.53
48	52	MW	0.4	0.131	4.27	0.024	0.81	0.5	0.117		0.018	
49	52	MW						2.1	0.079	2.90	0.025	0.91
50	52	FW	0.5	0.068	2.40	0.020	0.72					
51	53	MW						4.0	0.065	2.34	0.017	0.62
52	53	MW						2.3	0.036	1.33	0.018	0.67
54	54	MW						2.1	0.068	2.22	0.010	0.34
56	57	MW						2.8	0.075	2.46	0.015	0.48
57	57	MW	0.1	0.045	0.75	0.019	0.33	2.1	0.031	0.96	0.015	0.45
58	58	MW						1.1	0.015	0.39	0.008	0.22
59	58	MW	0.2	0.086		0.027		2.5	0.072	2.35	0.021	0.70
60	59	MW						2.3	0.039	1.91	0.012	0.62
62	59	FW						3.5	0.050	2.50	0.014	0.69
	Mean		0.5	0.084	2.47	0.024	0.70	2.4	0.066	2.18	0.016	0.57
64	61	FW						2.2	0.144	5.28	0.013	0.48
66	62	FW	0.9	0.098		0.021						
68	63	MW						1.7	0.019		0.013	
69	63	MW						2.0	0.098	3.05	0.023	0.70
70	63	MW	0.1	0.174	6.00	0.023	0.79	0.3	0.167	5.50	0.024	0.79
75	65	MW						3.8	0.061	2.55	0.019	0.80
76	65	MW	0.3	0.129	3.88	0.012	0.35	1.0	0.088	2.16	0.014	0.33
79	67	MW		0.104		0.011		2.9	0.054	2.61	0.016	0.79

TABLE 4. (Continued).

No.	Age (Years)	Sex, Race	Normal Coronary Artery Tissue					Arteriosclerotic Coronary Artery Tissue				
			Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour	Cholesterol, % of Wet Weight	Glucose-6-phosphate Metab., mM/Gm. Wet Tissue/Hour	Glucose-6-phosphate Metab., mM/Gm. Tissue N/Hour	6-Phosphogluconate Metab., mM/Gm. Wet Tissue/Hour	6-Phosphogluconate Metab., mM/Gm. Tissue N/Hour
80	68	MW						3.8	0.015	0.63	0.014	0.58
Mean.....			0.4	0.126	4.94	0.017	0.57	2.2	0.081	3.10	0.017	0.64
83	73	FW	0.2	0.087	3.05	0.013	0.45	1.4	0.047		0.015	
84	75	FW	1.2	0.077	2.96	0.017	0.65	4.0	0.047	1.62	0.021	0.73
Mean.....			0.7	0.082	3.01	0.015	0.55	2.7	0.047	1.62	0.018	0.73
Grand Mean*.....			0.4	0.089	2.93	0.021	0.62	2.3	0.071	2.51	0.018	0.64

* Excluding 0-5 year group.

women were 86% of those found for the men, both when expressed on the basis of wet tissue weight and tissue nitrogen content.

6-Phosphogluconate Dehydrogenase — The average quantity of 6-phosphogluconate metabolized by the pulmonary artery tissue (table 1) was 0.011 mM/Gm. wet tissue/hour for the samples obtained from children, and 0.015 mM for the samples from adults. The corresponding values, expressed on the basis of tissue nitrogen content, were 0.27 and 0.43 mM. No significant variation in enzyme activity with age was noted for the samples from adults (table 2). The mean values found for the women were 87% of those observed for the men, both when calculated on the basis of wet tissue weight and tissue nitrogen content.

Coronary Artery Samples

I. Normal Coronary Artery Tissue

Glucose-6-Phosphate Dehydrogenase — The average quantity of glucose-6-phosphate metabolized by 28 samples of normal coronary artery tissue from individuals aged 16-75 years was 0.089 mM/Gm. wet tissue/hour, and 2.93 mM/Gm. tissue nitrogen/hour (table 4). These values are, respectively, 94 and 113% of the G-6-PDH activities of the samples of normal aortic tissue from the same individuals. As seen from table 2 no significant change in the G-6-PDH activity of the coronary artery samples with age was observed.

6-Phosphogluconate Dehydrogenase — The mean quantity of 6-phosphogluconate metabolized by the normal coronary artery samples (table 4) from individuals aged 16-75 years was 0.021mM/Gm. wet tissue/hour, and 0.62 mM/Gm. tissue nitrogen/hour. It is of interest to note that these activities are more than twice as high as the activities of the normal aortic tissue samples from the same subjects (214%, expressed on the basis of wet tissue weight, and 243%, calculated on the basis of tissue nitrogen content). As in the case of the G-6-PDH no significant change in the 6-PGDH activity of the coronary artery samples with age was found (table 2).

II. Arteriosclerotic Coronary Artery Tissue

Enzyme activity measurements were made on 33 samples of arteriosclerotic coronary artery tissue (table 4); in only 17 of these samples was sufficient normal tissue obtainable to permit determinations also on normal segments of the arterial wall.

The average G-6-PDH activity of the 33 arteriosclerotic samples from persons aged 28-75 years was 0.071 mM/Gm. wet tissue/hour (2.51 mM/Gm. tissue nitrogen/hour) and the mean 6-PGDH activity 0.018 mM/Gm. wet tissue/hour (0.64 mM/Gm. tissue nitrogen/hour).

A comparison of the enzyme activities of arteriosclerotic and normal sections of the same arteries showed that the G-6-PDH activity of the arteriosclerotic tissues on the average was 74% of that of the normal tissue when expressed on the basis of wet tissue weight (t of difference, 4.17, N = 17), and 77% when calculated on the basis of the tissue nitrogen content (t of difference, 3.48, N = 11).

The difference between the 6-PGDH activity of the arteriosclerotic and normal coronary artery portions was found to be less marked, the mean activity of the arteriosclerotic tissue areas being 84% (wet tissue) and 91% (tissue nitrogen) of the activity of the normal segments. The t values of these differences are, respectively, 2.35 (N = 17) and 1.40 (N = 11).

DISCUSSION

The present study has demontrated the existence of notable activities of G-6-PDH and 6-PGDH in human arterial tissue, indicating the functioning in the tissue of the direct oxidative shunt. The extent to which the intact tissue utilizes this shunt as compared with the glycolytic pathway cannot be evaluated with certainty from the activity measurements performed on homogenized tissue samples. More precise information about this point might be obtained through investigations with glucose-1-C^{14} and glucose-6-C^{14}, as described by Bloom and Stetten (1, 2).

The G-6-PDH activity of normal aortic tissue observed in the present investigation is approximately 50% of that observed by Kuhlman and Lowry (4) for the rat brain.

It is of interest to note that the G-6-PDH activity of arterial samples obtained from children is only about ⅓ of the activity found in adult tissue. It should further be noticed that whereas the G-6-PDH activities of normal adult aortic, pulmonary artery, and coronary artery tissue were found to be of the same order of magnitude the 6-PGDH activity of the coronary artery was approximately twice that of the aortic tissue. This observation emphasizes the desirability of conducting enzyme investigations on different types of arteries.

The comparative studies performed on arteriosclerotic and normal tissue portions of the same aortic samples revealed markedly lower G-6-PDH activities of the arteriosclerotic segments of the vessels, whereas the difference in 6-PGDH activity was only moderate. A similar trend was noted with regard to the arteriosclerotic and normal coronary artery samples.

SUMMARY

Determinations were made of the glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase activities of homogenates of 85 samples of the aorta, 78 samples of the pulmonary artery and 45 samples of the coronary artery, obtained from individuals aged 0 to 85 years. In the case of the aortic and coronary artery samples the enzyme measurements were carried out both on normal and arteriosclerotic areas of the vessel wall.

The normal aortic tissue samples from adults metabolized an average of 0.108 mM glucose-6-phosphate/Gm. wet tissue/hour; the corresponding values for the pulmonary artery and normal coronary artery tissue were 0.081 and 0.089 mM. No significant variation in enzyme activity with age was observed for the samples from the 16 to 85 year old group. The glucose-6-phosphate dehydrogenase activities of aortic and pulmonary artery samples from children aged 0 to 5 years were found to be considerably lower than the activities recorded for adult arterial tissue, the mean values being 0.038 and 0.028 mM/Gm. wet tissue/hour.

The average 6-phosphogluconate dehydrogenase activities of normal aortic, pulmonary artery, and normal coronary artery tissue sample from adults were, respectively, 0.011, 0.015, and 0.021 mM/Gm. wet tissue/hour. In the case of this enzyme the activity values found for the samples from children were of the same order of magnitude as those observed for adult tissue, and no significant variation in enzyme activity with age was noted for the samples from adults.

A comparison of the mean activities of normal and arteriosclerotic tissue showed distinctly lower glucose-6-phosphate dehydrogenase values for the arteriosclerotic tissue, whereas the difference in 6-phosphogluconate dehydrogenase activity was only moderate.

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STUDIES ON THE METABOLISM OF THE MUCOPOLYSACCHARIDES OF HUMAN ARTERIAL TISSUE BY MEANS OF S^{35}, WITH SPECIAL REFERENCE TO CHANGES RELATED TO AGE

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To the author's knowledge, studies on the metabolism of the acid mucopolysaccharides (MPS) in human arterial tissue have not yet been reported. Certain aspects of the metabolism of sulfomucopolysaccharides may be investigated by S^{35}-labeled inorganic sulfate. When administered systematically as sulfate, 90% of the radioactive sulfate will be eliminated through the feces and urine within a few days (8, 9, 12), while the retained quantity is present almost exclusively in the sulfomucopolysaccharides and only negligible amounts as free sulfate (2) or reduced and incorporated in sulfur-containing amino acids (3, 23). Layton (19) performing *in vitro* experiments on tissue cultures, found that sulfate was not reduced to sulfides, but bound as sulfate. That the retained sulfate is present as sulfomucopolysaccharides has been substantiated in several studies using isolation of labeled sulfomucopolysaccharides from various tissues (4, 10, 11, 18, 20). By means of S^{35}-labeled inorganic sulfate, Layton and his associates (19, 20, 21, 22) studied the mucopolysaccharide metabolism in chickens and rats. His experiments showed that aortic tissue fixed considerable quantities of sulfate in insoluble compounds. Among the 10 investigated tissues only the epiphyses of the bones fixed the sulfate to a greater extent than aortic tissue. Buck and Heagy (5) performed similar experiments on rabbits that had been fed a normal diet and rabbits fed a cholesterol diet. Paper electrophoresis of alkaline extracts of cartilage, tendon, and aorta separated a peak of radioactivity which corresponded to a band that stained metachromatically with toluidine blue and was assumed to be chrondoitin sulfate. A significant elevation of both uptake of radioactive sulfate and the sulfur concentration was found in the aorta of the cholesterol-fed animals.

The present study forms a continuation of previous investigations concerning the mucopolysaccharides of human arterial tissue (7, 8, 15, 16, 17).

Its object was to make an attempt to develop a technique permitting determination of the sulfomucopolysaccharide metabolism in arterial tissue. If this attempt proved successful, the study was to be continued, investigating whether the mucopolysaccharide was subject to age variation, possibly related to the gross and microscopic signs of arteriosclerosis found in the arteries concerned.

METHOD

Sterile samples of human thoracic aortae were obtained, shortly after death, from the University Institute of Forensic Medicine, Copenhagen.* The adventitia was removed under sterile conditions, only the intima and media being used. Blood was removed as thoroughly as possible with sterile tampons. After 100-200 mg. of tissue had been reserved for dry-weight determination and histological examination, the remainder, representing the greater portion, was weighed, cut into very thin strips, and transferred to sterile Erlenmeyer flasks with glass stoppers. This was done in a box, protected from draught and dust. Most of the samples weighed about 5 Gm., but one, from a 4-month fetus, weighed only 88 mg. As a non-nutrient survival medium the author used a sterile Tyrode solution, modified by addition of non-radioactive sodium sulfate (10 mg./L.).

In all essentials, the Tyrode solution was prepared as described by Layton (19). About 5 ml. of Tyrode's solution was used per gram of

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wet tissue, and to this was added 1 mg. of streptomycin and 100 units of sodium penicillin per milliliter of the medium. Lastly, about 20 μc of S^{35}-labeled sodium sulfate per gram of aortic tissue was added, and the specimens were incubated at 38 C. for 45 hours.

After the incubation was completed, the specimens were inactivated by heating to about 60 C., and the mucopolysaccharides were isolated as described previously (7). Finally, the purified mucopolysaccharides were dissolved in 5 ml. of redistilled water. During the many steps of this procedure nearly all the radioactive inorganic sulfate was removed, but even so it proved necessary to remove the last traces by precipitation with 25% $BaCl_2$ solution. Three drops of this solution were added, the specimen was heated on a water bath to 85 C. for one hour, and the specimen was stored in the refrigerator overnight. The next day the specimens were centrifuged for 10 min. (3,000 r.p.m.) and were filtered through a Whatman filter No. 542. Another drop of $BaCl_2$ solution was added to ascertain whether all the inorganic sulfate had been precipiated. In these purified specimens the mucopolysaccharide content was determined by Di Ferrante's (14) method and the hexosamine content by the Elson & Morgan's (12) method, modified by Boas (1), as has been briefly described in a previous publication (15). However, all the volumes were reduced, partly to render the method more sensitive and partly to make the ultimate volume fit the cuvette of the Beckman D.U. spectrophotometer. The total volume for colorimetric determination was 4 ml. The hexosamine procedure was somewhat simplified; instead of the cumbersome neutralization of the hydrolysates, these were evaporated to dryness at 60 C. in a vacuum oven in the presence of

TABLE 1. UPTAKE OF RADIOSULFATE IN THE SULFOMUCOPOLYSACCHARIDES OF HUMAN AORTA.

No.	Age-Sex	State of Nutrition	Cause of Death	Macroscopic Arteriosclerosis	Microscopic Description of Degree of Arteriosclerosis*	% Dry Matter	Hexosamine % of MPS	Counts/Min. Mg. Hex./Hour† of Incubation
1	fetus ♂ 4 months			none				182.0
2	25 ♂	lean	traffic accident	slight	slight	33.0	28.2	29.0
3	29 ♂	lean	CO-poisoning	slight	slight	32.7	33.9	17.6
4	30 ♂	medium	CO-poisoning	slight	slight	31.6	25.1	24.7
5	35 ♂	lean	CO-ethanol poisoning	none	moderate	32.7	25.6 25.0	27.3 25.2
6	40 ♀	lean	CO-poisoning	slight	moderate	26.6	25.9 28.4	29.1 31.5
7	45 ♂	overweight	coronary-thrombosis	moderate	moderate	27.2	24.0	15.4
8	47 ♀	overweight	mb. cordis	moderate	slight	28.1	21.4	86.5
9	57 ♂	medium	mb. cordis	moderate	severe	29.5	26.2	9.5
10	59 ♀	medium	coronary-thrombosis	moderate		30.2	28.3	7.0
11	62 ♀	obese	pneumonia-pulmonary metastases	slight	severe	35.2	30.9	11.9
12	64 ♀	medium	mb. cordis	moderate		28.3	28.7 19.3	15.6 17.7
13	67 ♀	overweight	accident: fracture of the skull	moderate	severe	28.8	18.8	9.6
14	74 ♂	medium	mb. cordis	severe	moderate	31.2	29.7	4.1
15	80 ♂	obese	mb. cordis	severe		30.0	26.4	0
16	80 ♂	lean	suicide by hanging	moderate		34.0	—	4.9

* Stained metachromatically with toluidine blue.
"Slight": Swelling and metachromasia of intima.
"Moderate": Swelling and metachromasia of intima and media.
"Severe": Marked thickening and cell proliferation of intima.
Irregular distribution of metachromatic substances in media.

† Uptake of S^{35}-labeled sulfate calculated as counts per minute per mg. hexosamine in the isolated MPS per hour incubation.

magnesium perchlorate and NaOH. Finally, the radioactivity in the samples was measured by counting in a Geiger counter. A thin end-window (2.7 mg./square cm.) counting tube enclosed in a lead shield with a wall thickness of 5 cm. was used.

The counts were made in small metal counting pans with an internal diameter of 13 mm. with filter paper (A. G. Frisenette No. 641).

Counting was done on only a fraction of the sample, usually 200 μl., or 400 to 600 μl. in the case of the weak specimens. All counts were performed in duplicate after drying of the specimen in the counting pan. Nearly all the dried specimens weighed close to 2 mg., varying from 1.6 to 3.2 mg. Since S^{35} is a weak beta emitter, the self absorption was investigated, but no measurable self absorption was found under the present experimental conditions (fig. 1).

Control experiments were carried out in the case of 12 aortic specimens, one-half of each specimen being incubated at 0 C. or inactivated by heating to 60 C. before incubation at 38 C. Otherwise the specimens were treated in exactly the same way. These control experiments showed no uptake of labeled sulfate. This indicates that thermolabile enzymes are active in fixing the sulfate.

Since the specimens were incubated for a varying number of hours after death, the stability of the active enzymes was investigated.

In order to obtain comparable values, care was taken to make the ratio S^{35}/S^{32} in the incubation flasks the same in all experiments. A correction was made for the decay of the isotope, and the counts per minute were calculated per milligram hexosamine in the isloated mucopolysaccharides per hour of incubation. These findings are presented in table 1.

In experiments dividing the aortic specimens into portions incubated for varying periods (from 15 to 45 hours) or storing some of the specimens in the refrigerator for 24 hours prior to incubation, while incubating the other portion at once, the results showed that each individual aorta had the same uptake per time unit per milligram of hexosamine. In other words, the incorporation of sulfate was proportional to time of incubation and the enzymes were stable within the period of 45 hours. These findings agree with those of Curran and Gibson (6), who investigated the vitality of removed cartilage, using S^{35}-labeled sulfate. Cartilage maintained at 37 C. in Tyrode's solution proved to survive for 96 hours. When maintained in Tyrode's solution at 4 C. it survived for at least 40 days.

RESULTS

Table 1 and figure 2 present the results found in 16 human aortic specimens. Figure 2 shows the inverse relationship between incorporated sulfate and the individual's age. There is a distinctly decreasing intensity with advancing age, but quite a considerable individual scatter.

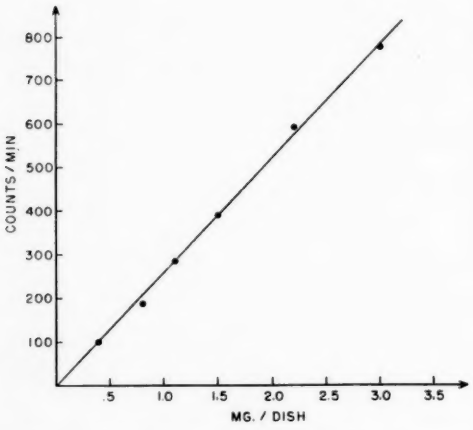

Fig. 1. Investigation of self absorption. Constant specific activity.

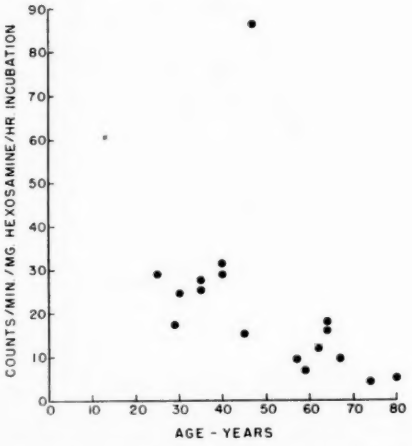

Fig. 2. Rate of uptake of S^{35}-labeled sulfate by aortic sulfomucopolysaccharides in individuals of various ages.

TABLE 2. RELATION BETWEEN GROSS AND MICROSCOPIC CHANGES AND THE UPTAKE OF S^{35} OF THE AORTIC SAMPLES FROM ADULT PERSONS.

Degree of Arteriosclerosis	Counts/min./mg. Hexosamine/Hour of Incubation	No. of Specimens	Degree of Arteriosclerosis	Counts/min./mg. Hexosamine/Hour of Incubation	No. of Specimens
None	26.3	1			
Slight	22.7	5	Slight	39.5	4
Moderate	21.3	7	Moderate	19.0	4
Severe	2.1	2	Severe	10.3	3

It is worth noticing that a specimen from a 4-month fetus showed a far higher activity than the specimens from adult persons (table 1).

Table 2 shows that aortae with grossly severe arteriosclerosis only fixed very little S^{35} as compared with the first three groups, which are almost alike. A pronounced relationship between microscopic changes and fixation of sulfate was also noted.

The total amount of hexosamine was studied in a number of the incubation fluids after the incubation. About 1 mg. of hexosamine per gram of tissue proved to have diffused into the aqueous phase in the course of 45 hours. It was impossible to ascertain in which chemical compounds this diffusible hexosamine occurred. That the material did not contain acid mucopolysaccharides was ascertained by the usual technique.

SUMMARY

The metabolism of the acid sulfomucopolysaccharides in human aortae was studied *in vitro* by means of S^{35} labeled inorganic sulfate. Sixteen samples were incubated with the radiosulfate, the mucopolysaccharides were isolated by chemical methods, and the uptake of S^{35} in the isolated material was determined. A decreasing uptake with increasing age and arteriosclerosis was observed.

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PHYSIOLOGICAL RESPONSES OF FIVE MIDDLE-AGED AND ELDERLY MEN TO REPEATED ADMINISTRATION OF THYROID STIMULATING HORMONE (THYROTROPIN; TSH)

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There are relatively few reported studies of responses to thyroid stimulating hormone (TSH; thyrotropin) in euthyroid humans, and, in these, age influences have not been explored. Only in the study by Martin and Stanbury (15) have ages of subjects been given for a study including more than one euthyroid subject. Of these, only three were free of demonstrable thyroid disease. Rall and co-workers (22) reported the effects of administration of TSH to a 71-year-old woman. Individual ages were not included in the reports of 9 euthyroid men, between the ages of 22-60 years, studied by Shipley and MacIntyre (24), and the "normal" subjects of Stanley and Astwood (31), some of whom were either receiving or had recently received thyroid or mercaptoimidazole. Other reports of thyroid response to TSH in euthyroid subjects do not include statements of ages or information on sex of the subjects (5, 7, 12, 14, 23, 30).

In humans, an increase in basal oxygen uptake (BMR), serum protein-bound iodine levels (PBI), and uptake of I^{131} by the thyroid gland have been reported followed the administration of thyroid stimulating hormone (7, 15, 20, 23, 31). Few euthyroid subjects, however, have been studied with simultaneous measurements of more than one index of response, or by measurements in the first several hours after I^{131} administration, as well as 24-hour uptakes. Moreover, studies have not compared the effect of TSH administration in repeated relatively large doses on different indices of thyroid function measured simultaneously. The present study was carried out to gain information on several physiological responses of middle-aged and elderly men to the repeated administration of thyroid stimulating hormone in doses larger than those necessary to produce detectable response in PBI and I^{131} uptake in most normal humans.

Since body water measurements have been found to be a useful parameter to which measurements of basal oxygen consumption may be related (25, 27, 28) and because body water compartments might be expected to be altered if body weight were changed on TSH administration, we measured the total and extracellular body water compartments before and after TSH.

MATERIALS AND METHODS

Subject Selection—Five ambulatory, reasonably healthy middle-aged and elderly men were selected from the Gerontology Ward of the Baltimore City Hospitals. Except for possible deviations specifically noted in the individual clinical evaluations given below, all fulfilled criteria designed to exclude individuals with thyroid or metabolic disturbances known to influence thyroid function. Individuals for whom it was felt that administration of the anticipated dosages of thyroid stimulating hormone might be hazardous were excluded.

In addition to the laboratory data (table 1), the major clinical criteria for selection of subjects are given below:

All subjects had been on the regular institutional diet for at least one month. Individuals demonstrating any of the following were excluded:

a. disease or injury to the thyroid gland or any portion of the so-called "pituitary-thyroid-adrenocortical axis" as evidenced by clinical history and physical examination; surgery in the region of the thyroid gland; therapeutic irradiation to the neck; palpable enlargement, mass, tenderness or elevation of skin temperature in the region of the thyroid gland.
b. advanced cardiac disease as evidenced by: angina pectoris; congestive failure; dyspnea (rate greater than 24/min. after 20 minutes rest in supine position); edema (see below); electrocardiographic evidence of previous myocardial infarction; or roent-

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TABLE 1. ANTHROPOMETRIC AND LABORATORY MEASUREMENTS ON SUBJECTS PRIOR TO TSH ADMINISTRATION.

	Subject				
	W. D.	L. G.	A. A.	W. L.	G. F.
Age (yrs.)	46	51	81	88	92
Height (cm.)	182.9	167.6	167.6	176.5	158.8
Weight (Kg.)	60.1	62.7	57.9	78.5	73.8
Surface Area (M^2)	1.68	1.71	1.65	1.94	1.75
BMR (cals./M^2/hr.)	35.8	32.6	33.0	31.5	30.6
BMR* (%)	+1.1	−5.2	+8.7	+3.8	+1.0
Serum PBI (μg. %)	5.7	5.1	7.1	5.9	5.8
I^{131} Uptake—24 hr.** (% dose)	44.7**	53.2**	48.0**	43.2**	32.2**
Total Body Water (AP) (liters)	34.2	31.9	32.0	34.9	29.8
Extracellular Water (liters)	16.3	15.5	14.6	18.5	16.5
Blood Pressure (R. A. supine) (mm. Hg)	115/74	118/80	163/82	140/67	144/80
Pulse Rate (basal) (beats/min.)	64	74	56	68	64
Hemoglobin (Gm.)	15.5	15.0	15.0	12.0	12.5
Hematocrit (%)	47.0	43.0	46.5	38.0	38.0
Sedimentation Rate—corrected (mm./hr.)	11	21	12	34	35
Leucocytes (N/$mm.^3$)	4800	4800	6400	8600	7100
Urine Specific Gravity	1.020	1.016	1.020	1.018	1.012
Fasting Blood Sugar (mg. %)	96	76	87	77	85
Non-protein N (mg. %)	24	26	31	45	29

* Calculated from weighted mean data grouped by age decades and compiled by Shock and Yiengst (26). Since the latter data do not include subjects of ages beyond 89, the expression of BMR as percentage for subject G. F. is based on the weighted mean for subjects of ages 80-89.

** Not corrected for radioactivity in thigh, the latter frequently used in attempt to correct for radioactivity in the circulation of the neck and not in the thyroid tissue. The values are within normal limits, based on results for a large number of subjects studied, using identical procedure, by Gaffney, Gregerman, and Shock (8).

genographic heart size more than 20% greater than normal limits for transverse cardiac diameter, according to standard height and weight tables.

c. incapacitating pulmonary disease as evidenced by dyspnea at rest (see above).

d. active renal disease as evidenced by $> 1+$ albuminuria (heat + acetic acid test), > 3 rbc/HPF, > 3 granular or rbc casts/LPF, or > 10 wbc/HPF.

e. hepatic disease as evidenced by: jaundice or icteric sclerae; hepatomegaly; abnormal firmness or nodularity of the liver detectable on palpation; prominence of veins on chest or abdomen; spider angiomata; or ascites (see below).

f. altered fluid volume as evidenced by: pitting edema of extremities or sacrum greater than 1+ (minimal); ascites as demonstrated by a fluid wave; or vomiting or diarrhea within one week prior to test.

g. blood pressure, after 20 minutes rest in recumbent position, greater than 180 mm. Hg. systolic or 90 mm. Hg. diastolic.

h. acute illness within one week characterized by oral temperature greater than 99.6° F., or excessive coughing or coryza.

i. administration of any drug or other agent (8) known to affect level of thyroid function, or measurement of: basal metabolism, accumulation of I^{131} by the thyroid gland or serum protein-bound iodine.

j. inability to cooperate in carrying out test procedures.

k. hematological abnormality as evidenced by: hemoglobin concentration of < 12 Gm./100 cc. or > 16 Gm./100 cc.; hematocrit $< 36\%$ or $> 48\%$; white blood cells < 3500/cu. mm. or $> 12{,}000$/cu. mm.; or abnormal differential wbc: neutrophiles $< 40\%$ or $> 90\%$, lymphocytes $> 45\%$, monocytes $> 20\%$, eosinophiles $> 7\%$, basophiles $> 3\%$.

l. diabetes mellitus evidenced by fasting blood sugar > 150 mg./100 cc., or glycosuria $> 1+$ on early morning specimen.

Clinical evaluations for the individual subjects, including physical examinations done just prior to the study, are abstracted below. None of the subjects suffered from perforation of the ear drums. Laboratory and anthropometric measurements are summarized in table 1.

W. D. was a 46-year-old Negro male with arrested bilateral upper lobe pulmonary tuberculosis, and sequelae of freezing injuries of the lower extremities. Tuberculosis had been diagnosed at age 33. The disease had been controlled and had been inactive for at least three years prior to the present study. At age 36, following exposure to cold, bilateral lumbar sympathectomy had been performed, followed by amputation of the right great toe and of the left leg below the knee. An adjustment of 6% was made in the calculated surface area of this subject for the amputation.

On physical examination, he appeared well. The thyroid was not enlarged. Fine inspiratory rales were present over the left upper lung field anteriorly. Operative scars were noted on the abdomen. The prostate was twice normal size. Indolent ulcers were noted at the base of the right second and third phalanges with trophic changes in the skin of the right leg and foot. He wore a prosthetic left leg.

There was no proteinuria, but urinary sediment showed occasional white and red blood cells. An electrocardiogram was normal except for broad, notched P waves. Chest x-ray revealed characteristic infiltration on the left mid- and right upper lung fields, unchanged in comparison with examinations made at intervals during the preceding three years. There was no cardiac enlargement. Bony changes were present in the right foot, but no osteomyelitis was noted. BMR, PBI and I^{131} uptake by the thyroid gland were within normal limits.

L. G. was a 51-year-old white male who had residual brain damage two years after recovery from acute syphilitic meningitis. A tendency to epileptiform seizures, which may have preceded his acute illness, was controled by phenobarbital and dilantin.

Physical examination was essentially negative except for some degree of impaired memory.

Blood and spinal fluid tests for syphilis remained positive. Peripheral blood smear revealed a relative lymphocytosis. Electrocardiogram showed a tendency to low "voltage" of QRS. X-ray of the chest revealed heart size to be within 5% of normal transverse diameter based on height-weight standard tables. Calcification was noted in the aortic arch.

Studies of BMR, PBI and I^{131} uptake by the thyroid gland were within normal limits (see footnote to table 1).

A. A., an 81-year-old white man, was in good health. Moderate emphysema, mild cardiovascular disease, and systolic hypertension had been observed for 7 years.

On physical examination, the thyroid was not enlarged. Breath sounds were distant. The heart was believed to be enlarged slightly to the left, and a blowing systolic murmur was noted at the apex. The prostate was enlarged. Slight dependent edema was occasionally present. There was a tremor of the upper extremities.

Blood smear examination revealed a 10% eosinophilia. Electrocardiographic pattern was compatible with left ventricular hypertrophy and enlargement. Chest x-ray was negative except for cardiac enlargement of 15% above normal transverse diameter based on height-weight standard tables.

BMR, PBI and thyroid I^{131} uptake studies were normal.

W. L. was 88 years of age. He was very deaf and apparently had been so since early childhood (etiology undetermined). He communicated only the grossest information about himself. For this reason, and due to the lack of records prior to his being admitted to the Infirmary and Gerontology Ward 4 years before the present study, his history is incomplete. He had, as a young man, sustained a probable compound fracture of the left femur without significant sequelae. There had been a successful cataract extraction. Varicosities of the legs and extensive osteoarthritis had occasionally given him trouble. There had been several episodes of mild cough without chest pain. Eighteen months, and again two months prior to the present study, he had febrile episodes with aggravated cough. Findings on the latter occasion were compatible with a pneumonitis on the right side.

On physical examination, he was noted to be large in build and somewhat slow in action. The thyroid gland was not enlarged. W. L. was sometimes observed to be somewhat short of breath, but had no complaints referable to his chest. Blood pressure was normal. The heart was at the upper limits of normal in size.

Urinalyses were negative except for microscopic hematuria on one occasion. Urinary specific gravity ranged from 1.010 to 1.018. NPN was 45 mg. %. Hematologic indices were normal. Differential blood smear showed 11% monocytes. Sedimentation rate was persistently elevated (34-35 mm./hr.). X-rays of the chest, taken just prior to the present study, showed clearing of the previously noted pneumonic process, although possibility remained of residual inflammatory disease. Heart size on x-ray had not changed in three years and transverse diameter was 12% above predicted normal for his height and weight according to standard tables. With one exception, the electrocardiogram remained unchanged, compared to records taken during the preceding three years, and was normal with occasional premature beats. The exception was the development of a prolongation of P-R interval to 0.24 secs.

In view of the scanty history on this subject, and the above observations, results of special function studies are of interest. Cardiovascular studies were carried out 2½ to 3 years prior to the present study. These revealed a resting cardiac index of 1.9 (in the lowest quartile of his age group), with a slow heart rate. Circulation time was 28 seconds (arm to tongue). Systolic blood presure was about 165 mm. Hg, but mean pressure was not significantly elevated. Thus, measures of cardiovascular function were, in general, poorer than those observed among his age equals. Pulmonary function studies showed evidence of a considerable reduction in ventilatory function with maximum breathing capacity of 38 L./min., vital capacity of 2.4 L., and a lung capacity of 5.72 L. Residual volume was 3.3 L.

It was clinically recognized, as well, that this subject evidenced some impairment in cardiopulmonary functions. Major clinical diagnoses were: mild pulmonary emphysema, with possible minimal fibrosis and bronchiectasis; arteriosclerotic heart disease (functional class II); atherosclerosis of the aorta and major arteries; bilateral deafness of undetermined etiology; retinitis pigmentosa; osteoarthritis, generalized; and varicose veins of the legs.

BMR, PBI and thyroid I^{131} uptake studies were within normal limits.

G. F. was a 92-year-old white male with Parkinsonism, asymptomatic mild cardiac disease presumably due to coronary arteriosclerosis, and benign prostatic hypertrophy. He had been admitted three months prior to the present study, with a recurrently draining sinus in the left anterior chest wall, the result of an abscess of unknown cause. Smear and culture revealed only *staph. albus* at this time. Except for nocturia and external hemorrhoids, which occasionally bled slightly, he felt well.

On physical examination, the thyroid gland was not enlarged. Slight gynecomastia was noted. The heart was slightly enlarged to the left, with a harsh, widely-heard systolic murmur. The penis was small, and the testes were atrophic. Bilateral inguinal herniae were present. The prostate was considerably enlarged. There was minimal bilateral dependent edema, and tremor of the upper extremities was noted.

Blood sedimentation rate was elevated. Electrocardiogram revealed a first degree AV block with a PR interval of 0.25 sec. ST was slightly depressed in leads, I, II, AV_1, V_5, and V_6. T waves were small. There were occasional premature ventricular systoles in one of two records. Although this record was abnormal, an electrocardiographic response to exercise was normal. X-rays of the chest and ribs showed no bony pathology. The transverse cardiac shadow was 15-20% oversize, and the left ventricular salient was prominent.

BMR, PBI and I^{131} uptake control measurements were within normal limits.

EXPERIMENTAL DESIGN

The study design included three periods: a control period of 49 days, a 5-day period of administration of 25 mg. (10 U.S.P. units) of thyroid stimulating hormone (TSH)* daily, and a recovery period of 112 days.

Basal oxygen uptake was measured weekly during the control period, daily for 5 days

* The authors are grateful to Armour Laboratories, Chicago, Illinois, for supplies of thyroid stimulating hormone used in the present studies. Data on the potency of the preparation used (Thytropar, Lot No. M2105) are the manufacturer's.

from the third day of TSH administration, and less frequently thereafter.

Blood for serum protein-bound iodine was obtained in the fasting state at least twice during the control period, at frequent intervals during, and for several days after the administration of TSH, and at least once during the recovery period.

Sodium iodide^{131} was administered for thyroid uptake studies about 4 weeks before TSH administration, after 4 days of TSH administration, and at least once 5 or more weeks later.*

Antipyrine and thiocyanate spaces were measured at the beginning of the control period, and 6 days after the TSH had been started (subsequent to I^{131} studies to avoid possible interference. See analytical methods below).

Resting heart rates and respiration were obtained in the basal state, and apical pulse rate and blood pressure were recorded at the time of clinical examination. All subjects were weighed and examined daily, before, during, and for several days to weeks following TSH administration. Electrocardiograms were taken as part of the clinical evaluation, and were repeated several times during, and after, the period of hormone administration.

ANALYTICAL METHODS

Estimates of BMR were made by the open circuit method (19). Three 10-minute periods, with duplicate gas analyses, were run. Mean values were computed for all 6 determinations. The standard error of the method, estimated from tests on different days in the same subject, was 1.7 cals./M^2/hr. (26).

Analyses of serum PBI were made by Bio-Science Laboratories, Los Angeles, California. The method used was a modification of the alkaline-ash method of Barker, Humphrey, and Soley (4), and gives results about 0.5 μg.% higher, on the average, than the original method. The modification used at Bio-Science differed from the original method in that only 0.5 cc. of 4 N Na_2CO_3 was added to the washed precipitate, and the tubes were dried in electrical heating blocks at about 100 C., followed by incineration at 600 C. for 30 min. (found adequate from time and temperature study). The ash was dissolved in an acid mixture containing sodium arsenite, water was added, and the mixture stirred and centrifuged. Samples were taken for colorimetry with ceric ammonium sulfate, the reaction taking place at 37 C. for 20 min. Recoveries were sufficiently close to 100%, so that no correction was needed for loss of iodine. The standard error of the method, estimated by Gaffney, and associates (9), from tests at an interval of 1-5 months (1-3 months in most cases) in each of 72 subjects, was 0.97 μg.%.

Estimates of thyroid uptake of I^{131} were carried out according to a procedure standardized for use in our laboratory (8), using 15 microcuries of carrier-free NaI^{131} (administered intravenously), scintillation detector and large collimator shield (10), lucite phantom for backscatter correction (33), and an optical focusing device, constructed in our laboratory, which made it possible to reproduce skin-to-crystal-center distance of 30 cm. within 1 mm. The interval between tests was sufficiently large to make it unnecessary to correct for residual I^{131} in the thyroid gland. Measurements were corrected for background and decay. Counts were such as to keep standard error, due to statistical counting sources, less than 2%. No attempt was made to correct any of the measurements for extra thyroidal I^{131} in the neck.

The uptake of I^{131} by the thyroid gland, expressed as percentage of the administered I^{131}, was determined at 4 and 24 hours. The standard errors of these determinations, as estimated by Gaffney, Gregerman, and Shock (8) from replicate determinations at an interval of 1-5 months (1-3 months in most cases) in each of a group of 69 subjects, were 4.2% and 8.3% for the 4 and 24-hour uptakes, respectively.

In addition, estimates of the time rate of change in the neck measurements for the interval of 1 to 4-6 hours after administration of the I^{131} were determined in each experiment. For this purpose, the slope of the best fitting line to the plot of percentage of dose (as "seen" by the collimated detector) against time was estimated by the method of least squares.*

* The present study was carried out under AEC authorization Nos. 32889 and 38870.

* Stanley and Astwood (31), as well as Perlmutter and Riggs (18), have followed a similar procedure for the calculation of an "accumulation gradient," except that their calculations were based on $t^{1/2}$. Gaffney, Gregerman, and Shock (8) have found that, for normal subjects and for the interval from 1 to 6-7 hours after intravenous administration of I^{131}, a linear fit to t is within the errors of measurement. Since the use of t permits interpretation of the slope of the curve as percentage dose accumulated per hour, and the plot is linear within the time limits considered, the simpler function seems preferable. The term "rate index" (8) has been given to this slope to distinguish it from the true rate of accumulation of radio-iodine by the thyroid gland, given by the slope only when neck measurements are *accurately* corrected for extrathyroidal radioiodine in the neck. A discussion of certain of the difficulties as-

The fit was based on 5-8 determinations in each experiment. The standard error of the "rate index" (8) constant, determined from duplicate tests in 50 subjects, was 0.6% per hour.

Estimates of total body water were made by the antipyrine method (29) and extracellular fluid space by the thiocyanate method (6). Details of the procedure, as adapted for use in our laboratory, have been reported by Shock, Watkin, and Yiengst (28). The standard error of measurement for total body water was 1.29 L., and for thiocyanate space 0.30 L. (28), based on repeated tests on the same subjects on two different days. The estimates of body water were carried out after, or at least 4 weeks before, I^{131} uptake determinations to avoid possible interference with the latter by thiocyanate or antipyrine.

Inhibition by thiocyanate of the thyroidal iodide concentrating mechanism is believed, by Wollman (35), to be competitive (on the basis of his experiments in mice). Data from our own and other laboratories indicate that the disappearance of thiocyanate from the blood is exponential (13, 27, 28), and that, 4 weeks after intravenous administration, its presence in plasma, or urine, cannot be detected (16). We have checked the effect of thiocyanate on the I^{131} uptake in one subject by obtaining a control thyroid I^{131} uptake in the normal range, and an uptake, one day after intravenous administration of 1.0 Gm. of thiocyanate ion, of very low level (never exceeding 6%, even at 24 hours). Three weeks later, in the same subject, I^{131} uptake pattern had returned to the control level. We are not aware of any data which would indicate any effect of antipyrine on the measurements of thyroid function under conditions we have used.

RESULTS

Clinical observations. All subjects evidenced clinical response to the administered drug, with increased heart rate and other signs of metabolic increment. After 48 hours on TSH, a slight tremor of the extremities developed, or was intensified, in all subjects. In three, slight diffuse thyroidal enlargement was detected (W. D., L. G., and A. A.), without tenderness or erythema. Insomnia occurred in two subjects, anorexia in two, while one (W. D.) noted increased appetite. Oral temperatures remained normal in the morning, but rose to less than 100 F. in the late afternoon in all subjects. (There was no evidence of local irritation, or inflammation, at site of injection.) Three subjects (W. D., G. F., and W. L.) developed, or showed an increase in the number of premature systoles, and, in W. D., A. A., and G. F., electrocardiographic T wave inversions occurred. Because of these, TSH was given for only 4 days to A. A. and G. F. The electrocardiographic changes occurring in these subjects on TSH administration are elsewhere discussed in detail (3).

Physiological responses to TSH administration. On the 2nd to 6th days after the starting of TSH administration, there was a measurable increase in each of the indices tested: pulse rate, BMR, PBI, and thyroid I^{131} uptake rates, as well as thyroid uptake of I^{131} at all times at which it was measured after the I^{131} was administered. The results for individual subjects are plotted in figures 1-5, and summarized in table 2.

Pulse rate reached a maximum within 9 days after the beginning of TSH administration, and receded to approach control values within the following 12 days. Maximum observed pulse rates ranged from 79 (A. A. and W. L.) to 103 beats/min. (L. G.), compared to control mean values ranging from 56 (A. A.) to 74 beats/min. (L. G.). Increases in pulse rate, above control values, were from 11 beats/min. (W. L.) to 38 beats/min. (W. D.).

Control values of BMR were normal, ranging from 30.6 (G. F.) to 35.8 cals./M^2/hr. (W. D.). Maximum observed increases in BMR, above control values, were from 7.7 (A. A.) to 17.3 (G. F.) cals./M^2/hr. Maximum observed values in BMR on TSH administration were reached in 2-9 days after TSH was started, and thereafter fell to control levels within the next 10-20 days. Once control levels were approached, there was no systematic pattern of rise or fall in BMR to suggest "compensatory" change during the period after TSH.

Control serum PBI levels were in the range of 5.1 μg.% (L. G.) to 7.1 μg.% (A. A.). On TSH administration, serum PBI levels increased in all subjects to maximum observed values in the range of 12.0 μg.% (L. G.) to 16.6 μg.% (W. D.) within 4-5 days after TSH

sociated with this correction, as well as data on variation in neck/thigh ratios with time after I^{131} administration, has appeared since the present paper was prepared (Goolden, A. W., and J. W. Mallard: A Method of Correction for Extrathyroidal Radioactivity. *Brit. J. Radiol.*, *31*, 41-44, 1958).

was started. The number and sequence of PBI values was not adequate to establish magnitude and time of peak PBI response. The smallest observed increase above control level was 6.9 μg.% (L. G.), while the largest was 10.9 μg.% (W. D.).

Thyroid I^{131} uptake studies, started on the 4th or 5th day of TSH stimulation, uniformly showed marked increases compared to control values. The data obtained for a 92-year-old subject are shown in figure 6. The accumulation rate index, representing an approximation of the rate of accumulation of I^{131} by the thy-

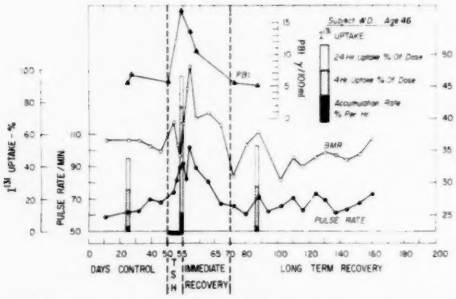

Fig. 1. Responses to thyroid stimulating hormone in a 46-year-old subject (W. D.). Each of the measurements of response to thyroid stimulating hormone (TSH) used in the present study is plotted against the number of days elapsed. The first 49 days represent the control period. On days 50-54, the subject received daily, for 5 days, an injection of 25 mg. (10 U.S.P. units) of TSH. (See clinical observations.)

Units: Pulse rate, beats/min.; BMR, cals./M²/hr.; PBI, μg.%; thyroid I^{131} uptake rate, % dose/hr.; thyroid I^{131} uptake at 4 hrs. and 24 hrs., % dose. (I^{131} measurements uncorrected for extrathyroidal radioiodine in the neck. See footnote on page 40, column 2 and 41, column 1.

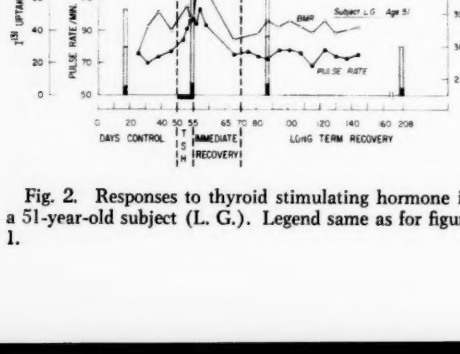

Fig. 2. Responses to thyroid stimulating hormone in a 51-year-old subject (L. G.). Legend same as for figure 1.

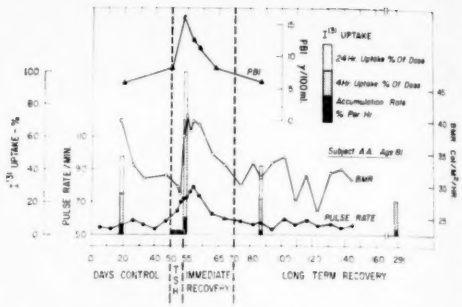

Fig. 3. Responses to thyroid stimulating hormone in a 81-year-old subject (A. A.). Administration of TSH was discontinued after 4 days for reason of appearance of medical contraindications to continued administration. Legend same as for figure 1.

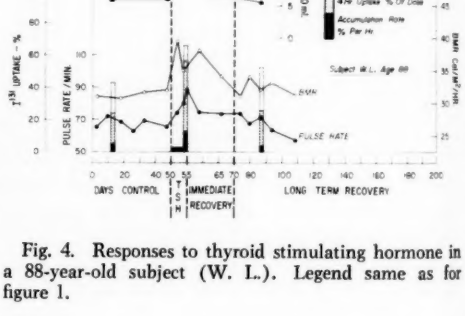

Fig. 4. Responses to thyroid stimulating hormone in a 88-year-old subject (W. L.). Legend same as for figure 1.

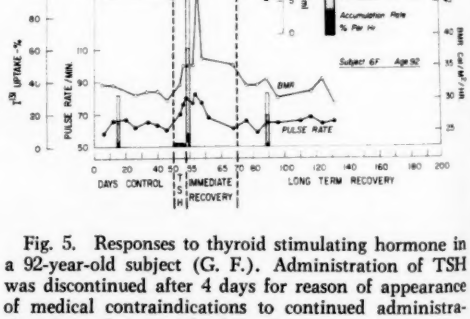

Fig. 5. Responses to thyroid stimulating hormone in a 92-year-old subject (G. F.). Administration of TSH was discontinued after 4 days for reason of appearance of medical contraindications to continued administration. Legend same as for figure 1.

TABLE 2. MAXIMUM RESPONSES TO TSH.

	Subject				
	W. D.	L. G.	A. A.	W. L.	G. F.
Age (yrs.)	46	51	81	88	92
Basal Pulse Rate (beats/min.)					
Control*	64	74	56	68	64
Max. Observed after TSH	102	103	79	79	82
Increment	38	29	23	11	18
Day of Maximum†	7	7	7	4	7
Blood Pressure (mm. Hg)					
Control*	115/74	118/80	163/82	140/67	144/80
Max. Observed after TSH	134/88	120/74	195/97	152/75	139/72
Increment	19/14	2/–6	32/15	12/8	–5/–8
Day of Maximum†	6	2	6	2	2
Basal Metabolism (cal./M²/hr.)					
Control*	35.8	32.6	33.0	31.5	30.6
Max. Observed after TSH	48.3	40.6	40.7	39.9	47.9
Increment	12.5	8.0	7.7	8.4	17.3
Day of Maximum†	7	7	5-7	2-9	7
Serum PBI (μg./100 ml.)					
Control	5.7	5.1	7.1	5.9	5.8
Max. Observed after TSH	16.6	12.0	16.0	13.3	13.6
Increment	10.9	6.9	8.9	7.4	7.8
Day of Maximum†	4	4	4	4	4
I^{131} Accumulation Rate Index (%/hr.)					
Control	3.6	5.0	6.3	4.5	2.5
After TSH	11.6	7.5	9.4	12.1	7.7
Increment	8.0	2.5	3.1	7.6	5.2
I^{131} 4-hour Uptake					
Control	26.0	30.0	25.5	23.5	14.8
After TSH	77.5	65.3	70.3	56.0	61.0
Increment	51.5	35.3	44.8	32.5	46.2
I^{131} 24-hour Uptake (% adm. dose)					
Control	44.7	53.2	48.0	43.2	32.2
After TSH	96.7	73.6	100.0	65.0	91.7
Increment	52.0	20.4	52.0	21.8	59.5
Body Weight (Kg.)					
Control‡	60.1	62.7	57.9	78.5	73.8
Max. Change after TSH	57.3	59.8	55.3	76.8	73.3
Decrement	2.8	2.9	2.6	1.7	0.5
Day of Maximum Change†	11	13	12	12	17

* Mean of 5 determinations made during BMR tests at one-week intervals prior to administration of TSH.
† Counting first day of TSH administration as Day O.
‡ Weight on day TSH administration was started.

roid gland in the interval from 1 to 4-6 hours after intravenous administration of I^{131}, and expressed as "percentage of dose accumulated per hour," increased in all subjects from control range of 2.5%/hr. (G. F.) to 6.3%/hr. (A. A.), to a range (on the 4th day of TSH administration) of 7.5%/hr. (L. G.) to 12.1%/hr. (W. L.).

Uptake of I^{131} by the thyroid gland at 4 hours after administration of I^{131} was greatly increased in all subjects after 4-5 days of TSH administration, as compared to control values (fig. 1-5). On TSH administration, the 4-hour thyroid uptakes of I^{131} ranged from 56.0% (W. L.) to 77.5% (W. D.), compared to control values ranging from 14.8% (G. F.) to 30.0% (L. G.). Increments above control values for 4-hour uptakes ranged from 32.5% (W. L.) to 51.5% (W. D.).

After 4-5 days of TSH administration, 24-hour thyroid uptake of I^{131} ranged from 65.0% (W. L.) to 100.0% (A. A.), compared to control values ranging from 32.2% (G. F.) to 53.2% (L. G.). Increments above control values were in the range of 20.4% (L. G.) to 59.5% (G. F.).

In subjects on whom sufficient data were obtained to estimate time of peak levels (W. D. and A. A.), the "peripheral" target responses (pulse rate and BMR) seemed to lag behind the increment levels in PBI by 2-3 days.

Weight and body water measurements. During, and after, TSH administration, all subjects lost weight (table 2). In one (G. F.), the loss was erratic and insignificant. Losses of 1.7 Kg. (W. L.) to 2.9 Kg. (L. G.) occurred within 11-13 days after the beginning of the TSH administration, followed by gradual return to control levels during the following 8-20 days.

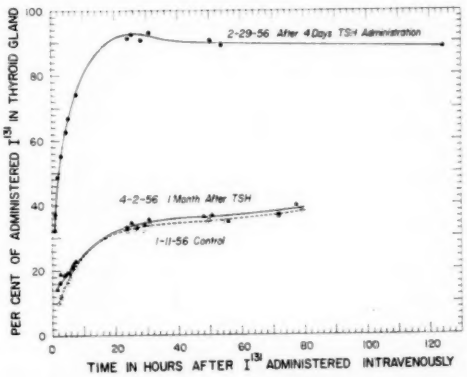

Fig. 6. Effect of thyroid stimulating hormone on I^{131} uptake by the thyroid gland in a 92-year-old man.

O Control I^{131} uptake. I^{131} administered on 1/11/56.

● TSH I^{131} uptake. I^{131} administered on 2/29/56 (after 4 days of TSH administration).

△ Followup I^{131} uptake. I^{131} administered on 4/2/56 (during recovery period).

In two of the subjects (W. D. and A. A.), it is probable that the weight loss was associated with the administration of TSH, since both had been showing a gradual rise in weight (55.6 to 60.1 Kg. for W. D. and 56.2 to 57.9 Kg. for A. A.) over the 6 months prior to TSH. Although two subjects were losing weight (67.8 Kg. to 62.7 Kg. for L. G. and 80.4 to 78.5 Kg. for W. L.) over the prior 6 months, their losses in weight proceeded at a greater rate in the 11-12 days following TSH administration than was true previously.

The loss in body weight was not accompanied by a reduction in antipyrine or thiocyanate volumes. Table 3 shows the antipyrine and thiocyanate spaces, as well as the body weights, taken on the same day the fluid spaces were determined. In two subjects (W. D. and G. F.), both antipyrine and thiocyanate volumes increased following TSH administration, although body weights did not change (W. D.) or increase (G. F.). In A. A., there was an increase in thiocyanate space, although body weights and antipyrine space were not altered significantly.

Blood pressure and respiration rate. Respiration rates were not significantly altered during, or after, TSH administration. The increments in basal metabolism were associated with an increase in tidal volume. Except for A. A., who showed an increase in both systolic and diastolic pressures, blood pressures were not systematically altered by the administration of TSH; that is, three subjects showed rises in both systolic and diastolic pressures, whereas blood pressures for the other two subjects were unchanged.

Age differences. The two subjects of ages 46 and 51 did not show responses generally different from those of the three men of ages 81, 88 and 92. With respect to pulse rate, the response was more marked for the younger subjects. The other indices (BMR, PBI and I^{131} uptake) yield nothing to support the contention of an age reduction in the responses to TSH. The maximum observed levels of PBI for the two middle-aged subjects (16.6 and 12.0 μg.%) were not substantially different from those of the elderly men (16.0, 13.3 and 13.6 μg.%). There is, moreover, no age difference apparent in the increments in PBI above control values (10.9 and 6.9 μg.% for the middle-aged, and 8.9, 7.4, and 7.8 μg.% for the elderly subjects).

Examination of the results on I^{131} uptake rate indices shows that the values on TSH for the middle-aged subjects (11.6 and 7.5%/hr.) do not differ substantially from those obtained for the elderly men (9.4, 12.1 and 7.7%/hr.). Similarly, the increases of the uptake rate indices, above control values on TSH, support no age pattern: 8.0 and 2.5%/hr. for the middle-aged versus 3.1, 7.6 and 5.2%/hr. for the elderly. Four-hour uptakes of I^{131} by the thyroid gland also suggest no age difference; the values on TSH for the middle-aged men (77.5 and 65.3%) were similar to those obtained for the elderly subjects (70.3, 56.0 and 61.0%), corresponding to increases on TSH, compared to control values, of 41.5 and 35.3% for the middle-aged versus 44.8, 32.5 and 46.2% for the elderly men. The story is the same for the 24-hour uptakes: uptakes on TSH for the middle-aged men (96.7 and 73.6%) compared with those for the elderly (100.0, 65.0 and 91.7%), corresponding to increase on TSH

TABLE 3. EFFECT OF TSH ADMINISTRATION ON BODY WATER COMPARTMENTS.

Subject	Age (Years)	Body Weight* (Kg.)		Total Body Water† (liters)		Extracellular Space‡ (liters)	
		Before TSH	After TSH	Before TSH	After TSH	Before TSH	After TSH
W. D.	46	58.2	58.8	34.2	36.6	16.3	18.5
L. G.	51	65.4	60.8	31.9	31.3	15.5	15.6
A. A.	81	56.7	56.6	32.0	30.5	14.6	16.0
W. L.	88	80.8	78.2	34.9§		18.5§	
G. F.	92	70.2	74.3	29.8	34.7	16.5	18.0
Mean		66.2	65.7	31.9	33.3	15.7	17.0

* Body weights given in this table were taken on the same day that fluid spaces were determined.
† Determined as antipyrine space.
‡ Determined as thiocyanate space.
§ Excluded in calculation of the mean.

above control values of 52.0 and 20.4% for the middle-aged versus 52.0, 21.8 and 59.5% for the elderly men.

DISCUSSION

The foregoing results, obtained on subjects administered 25 mg. of TSH on 4 or 5 successive days, are in substantial agreement with observations reported by others (7, 15, 23) for 25-50 mg. of TSH administered on 3-7 consecutive days.

Indices of response to thyroid stimulating hormone. In the absence of dose response information for repeated administration of TSH, it is not possible to determine whether or not the dosage schedule used for our subjects was adequate to obtain maximal responses of which their glands were capable. There may be some suggestion that such was not the case in the fact that PBI may have still been increasing when the TSH was discontinued. Moreover, in none of our subjects was the response nearly as marked as that observed by Gabrilove and Soffer (7) for administration of a dose twice as large, and for a longer period than we used. The doses we have used are large compared to the doses which have been used for diagnostic purposes to increase I^{131} uptake or PBI response in euthyroid individuals, but were not intended as maximal doses. Although PBI was not determined daily, the fact that maximum observed "peripheral responses" (pulse rate and BMR) lag by 2-3 days, the maximum observed values for PBI (in subjects W. D. and A. A.) suggests the possibility that the "peripheral responses" may be delayed by the time required for conversion of the hormones associated with the PBI to triiodothyronine, or other active derivatives at the "target" site.

Under the experimental conditions of the present study, the most responsive of the various indices considered were the PBI and I^{131} uptake at 4 hours (or other arbitrary interval less than about 6 or 8 hours). By "response" of an index (PBI, I^{131} uptake at 24 hours, etc.) to TSH stimulation, we here mean fractional increase of the index following TSH administration, compared to control levels; i.e., the ratio of increment on TSH to the control level. The PBI, the I^{131} accumulation rate index, and the 4-hour uptake of I^{131} showed a 2 to 3 fold increase following TSH. At 24 hours, however, the uptake without TSH stimulation climbed to near peak levels and the value, under strong TSH stimulation, may have fallen below peak value. The result is lower responsiveness of the 24-hour I^{131} uptake, relative to I^{131} uptake at less than about 4 hours, for detection of this type of TSH stimulation. The uptakes at earlier intervals more nearly represent the "rate" at which I^{131} is accumulated at the time when most of it is still available in the circulation.

Age changes. Reduction in the functional capacity of the thyroid gland, with increasing age, has been hypothesized, but rests on no substantial body of evidence. Although age changes in the morphology of the thyroid gland have been reported (2, 17), as well as a progressive decrease in basal oxygen consumption per square meter of surface area (26), other indices of thyroid function such as serum PBI (11, 18, 32, 34), the uptake of I^{131} by the thyroid gland (18, 21) or urinary excretion of I^{131} (1) have yielded equivocal results with respect to age changes. Even basal oxygen consumption measurements fail to show a decrement with age when expressed in terms of total body water content (25, 28).

The evidence in the above studies does not, in general, support the contention of an age-wise pattern in functional level, as distinct from morphology, of the thyroid gland. This suggests that either: 1) morphological changes observed with age do not involve, to any great extent, the sites essential to functions actually measured (and assumed to be correlated with function of the gland) at "resting" levels, or 2) the "reserve" of the gland is so large that losses in functional capacity with age are not reflected at "resting" levels of function by the methods so far used. For the doses we have used, moreover, the responses to TSH stimulation of the subjects of ages 81, 88, and 92 show no deficit compared to the younger men of ages 46 and 51. For those who would seek age differences, there remains the possibility of disclosing limitations in the functional capacity of the thyroid gland under conditions of maximal stimulation. There also remains the possibility that other techniques, perhaps not involving variables affecting results obtained by methods used so far, may disclose age differences even for the functional level of the "resting" gland.

Weight changes and body water compartment. In 4 of the 5 subjects, there was evidence of a loss in body weight following the adminis-

tration of TSH. Since neither the total body water nor the extracellular fluid spaces fell, it is improbable that the weight loss can be ascribed to fluid losses. All but one of the subjects, for whom data were obtained, showed an increase in total body water, expressed as percentage of body weight. In these subjects, the loss in weight must have been at the expense of non-aqueous components such as fat or tissue protein.

SUMMARY

In two middle-aged (ages 46 and 51) and three elderly (ages 81, 88, and 92) men, in reasonably good health and believed free of diseases and conditions affecting thyroid function or its measurement, various responses to administration of thyroid stimulating hormone (thyrotropin; TSH) have been estimated. Following a control period of 49 days, during which pulse rate, basal oxygen consumption (BMR), serum protein-bound iodine (PBI), and I^{131} thyroid uptake measurements were carried out, each subject received 25 mg. (10 U.S.P. units) of TSH daily for 4 or 5 days. At intervals during, and after, the period of TSH administration, measurements were repeated. By the 2nd to 6th days after the starting of TSH, there was, almost uniformly for each of the subjects, a measurable increase for each of the indices tested: pulse rate, BMR, PBI, and thyroid I^{131} uptake rate index and I^{131} uptake at 4 and 24 hours (not corrected for extrathyroidal radioiodine in the neck). With TSH administration, maximum observed increases above control values were: pulse rate, 11-38 beats/min.; BMR, 7.7-17.3 cals./M^2/hr.; PBI, 6.9-10.9 μg.%; thyroid I^{131} uptake rate index, 2.5-8.0%/hr.; 4-hour thyroid I^{131} uptake, 32.5-51.5%; 24-hour thyroid I^{131} uptake, 20.4-59.5% (I^{131} uptake tests were done after 4 days of TSH administration). Largest observed levels of PBI occurred about the 4th day, while the maximum increments in pulse rate and BMR occurred, in most cases, about the 6th or 7th day after TSH was started. Repeated measurements, made during the 9-week interval after TSH was discontinued, revealed a return to control levels with no evidence of systematic compensatory changes in any of the indices due to TSH administration.

Responses of the middle-aged subjects (ages 46 and 51) were not substantially different from those of the elderly men (ages 81, 88, and 92). The available evidence, which is meager, does not support the contention that, with advancing age, there is decreased responsiveness of the thyroid gland to TSH.

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EFFECTS OF AGE ON THE DISCRIMINATION OF LIFTED WEIGHTS*

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The purpose of this study is to examine the effect of age upon a number of variables involved in discrimination of weight differences (3). There are, however, implications in the present study for investigations in other sensory modalities and in general for explicating psychological research on aging.

On the average, the older organism has increasing difficulty in making discriminations among sensory stimuli and is slower to respond (1, 14). Amid the points not known at present is the extent to which the slowing of response speed of the older organism results from a deficit in perception; also it is not known whether the reported age changes in perception are modality specific or whether some general process is involved, the influence of which is manifest in many ways in all sensory modalities.

There is a class of age changes in the organism which increases the physical barriers between stimuli and receptors. Thus a smaller portion of the initial stimulus energy may, in the case of the eye, fail to reach the receptors because of, e.g., lens opacities, smaller pupils, and cloudy vitreous. In other sense organs, connective tissue changes associated with age can interfere with stimulation. Not all changes of interpolated interference with stimuli are necessarily correlated despite their joint correlation with age. Thus, a lens cataract is not necessarily associated with other impediments in vision, since its removal will often restore vision.

In addition to increased sensory "barrier effects" with age, "primary receptor" changes also may occur, some for exogenous reasons like interference with blood flow in the retina; others may exist because of the common nature of receptors as specialized neural tissue which may have a propensity to change with age, independent of the local environment. To these, however, should also be added the possibility of age-common and age-independent changes in "primary perception," those psychological processes by which we recognize or classify sensations permitting appropriate responses.

To protagonists of information theory there is an inherent attractiveness for the idea of exploring age changes in "channel capacity" or "information capacity" of the organism. In part the idea derives its attractiveness from the assumption that the notion of a channel is relevant to the flow of information in and out of the human organism. If there exists a single channel and if it has a finite capacity, then it should certainly be studied. But there may be many "channels" and their capacity may be less relevant in aging than the organism's ability to alter or to supersede stimulus-response units by combining. The important change with age may not be so much a reduced channel capacity as it is a change in what constitutes a unit in a skilled activity. For example, changes in motor skills with age as handwriting resemble a fragmentation of what previously was a unitary skill, i.e., the task is done piecemeal (1).

Gregory has advanced the hypothesis that with increased age there is greater noise in the nervous system (6). But here again one may ask, in addition to questioning the basic hypothesis, whether the noise is general or specific to a receptor. Crossman and Szafran (4) gave some emphasis to the Gregory hypothesis of reduced information capacity via an age change in signal to noise ratio. In their preliminary report they did not present evidence for a communality of performance on the two tasks studied, card sorting and weight lifting, e.g., correlation of individual performance, nor were tests made of the significance of the slopes of the functions in terms of the hypothesis.

Mention has been made of several relevant non-perceptual factors; among these is the criterion level or "level of confidence" the sub-

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ject requires before responding (8). In this sense the older subject may wait longer until he responds, thus registering his judgment, being less willing to act on percepts of equivalent strength. Also, all other things being equal, the older individual may show a greater transfer effect from a previous response to a present one, e.g., preservation. These possibilities do not seem to explain readily, however, the tendency of older persons to attend to specific or concrete details of complex stimuli rather than to abstractions (12).

We still are unable to state whether age changes occur equally: whether there is a correlation of absolute thresholds, difference limens, and speed of perception or response. Studies of these relations should give us an increasingly precise idea of the nature of the processes of aging. Before such integrated information is obtained, however, more limited studies, such as the present one on weight lifting, are necessary to describe the range of phenomenon and for preliminary sorting of suspected pertinent variables.

In the present study the ability to discriminate weights was measured for both simultaneous and successive discrimination for old and young subjects. For both cases three different experimental conditions were used to introduce the effects of time. In addition to the measurement of the ability to discriminate under the prescribed conditions, measurements were made of the following variables: acceptance or equality, bias, preservation, reaction time, and variability.

EXPERIMENTAL PROCEDURES

Duplicated sets of weights 100, 105, 110, and, 115 Gm., each with a 100 Gm. standard were prepared from ¾″ dia. brass rod, each being 2⅛″ long. The weights were symmetric and were adjusted to weight by drilling into each end. All weights had the ends sealed and were then painted and coded at one end.

Each series of 16 weights was presented in a prescribed order. The subject was seated behind a screen with hands protruding through holes and arms comfortably supported. Weights were placed into the hands of the subjects about 2 sec. after a verbal warning, "ready." In some experimental situations, reaction times were recorded. The observer depressed a foot switch connected to a timer when the weights were released on the subjects' hands and quickly released the foot switch when a response was given. Except for some subjects who responded very much more rapidly than the average, the systematic error and the error in variability introduced by the observer is not important. If we are primarily interested in age differences, the error becomes even less important.

A group of 42 older subjects was compared in performance with a group of 39 younger subjects. The former group ranged in age from 58 to 85 with a median age of 74. The younger group ranged in age from 18 to 32, with a median age of 24 years. In the younger group 19 were employees of the National Institutes of Health and 20 were enlisted army personnel. In the elderly group 19 were residents of the Soldiers Home, Washington, D. C., and 23 were residents of the Home for the Jewish Aged, Philadelphia.

Each subject was given each of 10 series of discriminations for which the procedures were as follows:

1. Simultaneous discrimination, three category, normal set. "As soon as you think that one weight is heavier than the other say 'left' or 'right' depending on which hand has the heavier weight. If you think they are the same say 'same.' Do not rush, but give your first impression." Reaction time recorded.

2. Successive, left hand, 2 sec. delay, each stimulus left on hand for 2 sec. Instructions as in (1) except "first" and "second" replace "left" and "right."

3. Successive, right hand, 2 sec. delay, each stimulus left for 2 seconds on hand. Instructions same as for 2.

4. Successive, right hand, 10 sec. delay, otherwise same as 3.

5. Repetition of 1.

6. Simultaneous, two category, normal. "As soon as you think that one weight is heavier than the other say 'left' or 'right' depending on which hand has the heavier weight. You must say either 'left' or 'right.' If uncertain, you may guess." Reaction time recorded.

7. Simultaneous, two category, fast. "We now want to see how fast you can respond correctly. Say 'left' or 'right' as fast as you can tell which is heavier. You will be timed." Reaction time recorded.

8. Simultaneous, two category, time limited. Weights in hands about 1 sec. Instructions

same as 6, except that the subjects were told that the weights would be removed.

9. Long sequence perseveration. Starting with a +20 Gm. difference, then +15, +10, +5, 0, −5, −10, −15, −10, −5, 0, +5, +10, +15. Instructions the same as for 6.

10. Repetition of 6.

Each series was preceded with a few practice trials. The subjects were not told how they were performing but were told that they were following the instructions very well if they seemed to need encouragement. This was especially necessary for some of the older subjects. The tests were given in the order listed above except that tests 2, 3, and 4 were also given in the order 4, 3, and 2; and similarly for tests 7, 8, and 9.

RESULTS

Discrimination. The results of measurements of the ability to discriminate weights are shown in table 1. The values given are the average discrimination scores defined as the total for 5, 10, and 15 Gm. differences of the total correct minus wrong divided by the total correct and wrong, exclusive of "same" judgments. If these values are divided by 20 they represent the average slope of the percentage correct as a function of grams difference, i.e., $\triangle P_c / \triangle w$.

It can be seen from the results in table 1 that, for simultaneous discrimination, the relative performance of older to younger is about 70% for the normal speed and about 60% for the cases of increased tempo. On the other hand, in the case of successive discrimination, the younger are only slightly superior to the older subjects in each of the three experimental situations. The age differences in the individual instructions are not significant. In neither group did an increase from 2 sec. to 10 sec. in the delay between first and second stimulus produce a significant decrease in performance. Perhaps an interval substantially longer than 10 sec. would be required to test for the possibility that the older subject may be more influenced by long delays than younger subjects.

Some subjects may *need* a long time in reaching a judgment rather than *want* a long time. The possibility was considered that the individuals who showed the greatest decrease in performance when told to respond as fast as possible were also the ones who showed the greatest decrease when given a short time for judgment. A test of this possibility showed that for the older group there was a correlation of 0.43 ($t = 3.4$), while for the younger group the correlation was 0.48 ($t = 3.8$), both results being significant.

When the proportions of correct responses are plotted against the grams difference for the two and three category cases of the normal-speed simultaneous-discrimination, the results shown in figure 1 are obtained. The lines in the figure are drawn through the weighted average of the points.

It can be seen that the older subjects are not appreciably more variable than the younger subjects. However, on a relative basis they are more variable in the simultaneous discrimination situation. Note that the performance of the older subjects is very much poorer in these cases.

TABLE 1. DISCRIMINATION SCORES (IN %).

Test Condition	N	Younger Discrimination S. D.	N	Older Discrimination S. D.	O/Y ± S.E.
Simultaneous					
Normal [2]*	932	44 ± 17	996	28 ± 20	0.64 ± .1— 2
Normal [3]*	733	44 ± 23	785	33 ± 23	0.75 ± .10
Fast	468	37 ± 23	504	22 ± 26	0.60 ± .10
Time Limited	468	32 ± 23	504	17 ± 22	0.54 ± .13
Successive					
Left Hand	353	49 ± 33	370	47 ± 31	0.95 ± .14
Right Hand	359	51 ± 31	382	48 ± 27	0.93 ± .12
Right Hand (10 sec. delay)	364	49 ± 29	399	45 ± 28	0.92 ± .13

* Numbers refer to procedures listed under Experimental Procedures.

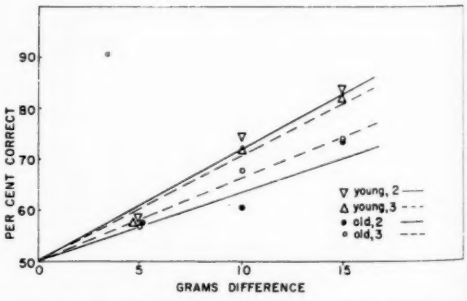

Fig. 1. Percentage of correct responses as a function of the difference in the two lifted weights. Data are given for simultaneous discrimination, two category ("right" or "left"); three category ("right," "left," or "same"). Lines are plotted through weighted average.

TABLE 2. AVERAGE PERCENTAGE ACCEPTANCE OF EQUALITY.

Test Condition	Younger	Older	Difference Y – O
Simultaneous (normal)	26.8	24.7	2.1
Successive Left Hand	24.7	27.8	– 3.1
Right Hand	26.2	26.0	0.2
Right Hand (delay)	22.9	21.9	1.0

Acceptance of equality. The results of the present experiments do not show any appreciable age difference in any of the situations tested as can be seen in table 2. Here the average percentage "same" judgments from 0 and 5 Gm. differences are shown. The data for simultaneous discrimination, normal rate, are given in figure 2 in which the percentage of "same" judgments is plotted against 0.7 times the weight difference, 0.7 being the average value of the O/Y ratio in the upper half of table 1 for "normal" situations. It can be seen that when difficulty is corrected for, the older group used slightly less "same" judgments throughout the range of weight differences. However, since the number of subjects is relatively small no claim is made that this difference is significant.

If the percentages of "same" judgments are plotted against corresponding percentages correct, one finds that the curves for older and younger are quite similar, except for a tendency for the data on younger subjects to peak near the center of the curve. The data for both groups can be satisfactorily represented by a theoretical curve for constant threshold, h = 0.33 (9). The data of Urban (13) have been shown to be consistent with such a theoretical curve with threshold (9).

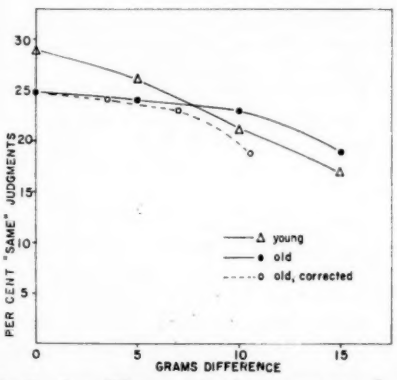

Fig. 2. Age differences in the percentage of equal judgments ("same") as a function of the difference in the two weights.

Bias. The bias for each subject in each situation was calculated from the raw data. Positive values were defined as favoring the "right hand" response in simultaneous discrimination or the "second" response in the successive judgments. The values were calculated from 0 and 5 Gm. differences using the relation

$$\text{Bias} = P_R - 50, \text{ or } P_2 - 50,$$

where P_R and P_2 are the percentages of "right" or "second" judgments, excluding the "same" responses. A distortion is introduced due to differences in ability to discriminate. However, since the average values are so small, this distortion is ignored. The average biases for the two groups are shown in table 3 together with the standard deviations.

It can be seen from the table that age differences are insignificant. The only significant differences from zero are the delayed right hand values, but these are about the same for both groups. The older subjects are significantly more variable than the younger in the case of simultaneous discrimination.

In order to estimate to what extent a bias is maintained from test to test the correlation between the tests 6 and 10 was obtained for both older and younger subjects. When all items were used to estimate the bias, the values of the correlation were found to be, respectively, 0.72 and 0.67. For the observed distribution of bias one cannot expect a correlation greater than about 0.8 as a result of the individual values being determined from only 16 judgments. When this is considered, the correlations can be seen to be fairly high.

Perseveration. It is convenient to divide systematic errors into those which are essentially

TABLE 3. BIAS.*

Test Condition		Older	Younger
Simultaneous	Two Category	0.02 ± .32	−0.02 ± .24
	Three Category	−0.04 ± .34	−0.05 ± .24
Successive (3 category)	Left Hand	0.07 ± .27	0.01 ± .26
	Right Hand	0.02 ± .29	0.08 ± .26
	Right Hand (delay)	0.18 ± .25	0.21 ± .23

* Positive bias values were defined as favoring the "right hand" response in simultaneous discrimination or the "second" response in the successive judgments.

time independent over an experimental interval and those effects which change relatively rapidly. The former we have referred to as bias. The latter we shall refer to as perseveration.

Two measurements of perseveration were made on each subject. For the first, test 9 was scored as follows:

$2\varrho_l = P_R$ (descending half sequence) $- P_R$ (ascending half sequence), in which the symbol P_R represents the proportion of "R" responses. The above difference represents the area within the closed curve, or hysteresis loop. This gives a measure or perseveration over the entire set of judgments and is referred to as $2\varrho_l$ in table 4. It can be seen that for these judgments there is no appreciable perseveration for either older or younger over a series of this length.

A second measurement, also given in table 4, is a short term perseveration. This is obtained from two items on each test. One is a zero gram difference following a +15, +10 Gm. difference sequence while the second is a zero Gm. difference following a −15 Gm. difference. The short term perseverance can be scored separately for the persistence following a wrong judgment ($2\varrho_w$) and for that following a correct response ($2\varrho_c$). For example, the values of $2\varrho_w$ are obtained from only these judgments on equal stimuli which immediately follow a wrong response, "same" responses being omitted. Each value is the proportion of responses which are the same as the previous response minus the proportion which are opposite the previous response. The values for ($2\varrho_c$) and ($2\varrho_t$) are similarly defined, the latter being the weighted average of the other two.

Two kinds of short term perseveration can be thought of as contributing to the observed response (10). First there may be a component which depends only on the judgment. Thus, having made a judgment "left" (hand), the next judgment is more probably "left" due to this effect. This would give a value which does not depend on whether the previous response was correct or wrong, unless one postulates that there exists a subconscious judgment which is more accurate than the verbalized judgment. We shall refer to this as perseveration of response. A second kind of perseveration can arise if the spontaneous fluctuations causing variability have a residual effect in the next judgment. In this case the observed response will be different for the responses following wrong and correct judgments and will depend on the ability to discriminate. Since we can think of the fluctuation as a temporary bias, we shall refer to this as perseveration of bias.

It can be seen from the tabled values that the older subjects perseverate more than do the younger when compared in terms of the indices following correct, wrong, or total judgments. It can be seen that the first kind of perseveration is not as satisfactory an explanation for the data on the old subjects and is not at all satisfactory in the case of the data on the younger subjects. It is necessary to consider the results to be expected on the basis of the two kinds of perseveration. The theory of these effects is treated in detail elsewhere (10).

If the bias is not too great it can be corrected for (9, equation 10). Seven subjects in each group showed extreme bias. When these are removed, then instead of the values 0.39, 0.24; 0.33, −0.07 given in table 4, we obtain 0.29, 0.21; 0.25, −0.10.

For the older subjects the data are compatible with either type of perseveration, though a composite is more likely. Correcting for the mean square bias, $\overline{\epsilon^2} = 0.035$, the values 0.29 and 0.21 become 0.26 and 0.19. From these values and using equations 8 and 9 of reference (10) we obtain f = 0.14 and r = 0.17, these values corresponding to about 3 and 4 Gm., respectively. The first value is a measure of perseveration of bias, the second is a measure of perseveration of response. The value in grams corresponding to f is that amount in grams which would have to be added to one of the equal pairs to produce the observed response when the conditioning stimuli are equal. These values are very approximate and are given mostly to illustrate how the two effects can in principle be separated.

TABLE 4. PERSEVERATION.*

Index of Preservation	Younger	Older	"t" (Y–O)
$2\varrho_t$ (long term)	−0.05±0.20	−0.03±0.24	—
$2\varrho_w$ (short, after "wrong")	0.33±0.48	0.39±0.50	—
$2\varrho_c$ (short, after "correct")	−0.07±0.27	0.24±0.28	5
$2\varrho_t$ (short, total)	0.02±0.30	0.29±0.31	4
Correlation (ρ_w, ρ_c)	0.38 (t=2.8)	0.35 (t=2.6)	

* Perseveration is defined as the persistence of a response over a set of judgments.

For the younger subjects the data are hardly compatible with either type of perseveration alone. Correcting for bias $\bar{\varepsilon^2} = 0.033$, the values 0.25 and -0.10 become 0.21 and -0.11. From these values we obtain $f = 0.14$ and $r = -0.17$ which corresponds to 2 and -3 Gm., respectively. These values are also very approximate, but the pattern for the younger is evidently quite different from that of the older subjects. The perseveration of response is opposite in the two groups.

Reaction time. After 5 sets of trials it would be expected that each subject would have adopted a natural tempo. Hence the reaction times of older and younger subjects were compared for the normal, two category case of test 6. These values are shown in table 5. Also included are the reaction times of test 7 for the "fast" set. It may be noted that the O – Y difference is about the same for both sets. In all cases in which variability was measured, the older subjects were considerably more variable than the younger subjects, but when compared on a basis relative to the mean, the older group showed a smaller variability, though not significantly so, 0.55 vs. 0.68.

Also shown in table 5 are the differences between reaction times from test 6 and its duplicate test 10. Between these two tests there were a "fast" and a time limited test. The values therefore represent a carrying over of these intervening sets. Note that the older and younger groups gave about the same decreases on a relative basis.

Measurements of reaction times are given in relation to weight difference in figure 3. The correct and wrong responses are given separately for both older and younger subjects. In neither group is the reaction time appreciably altered by task difficulty over the range used. The younger group is, on the average, faster by 0.5 sec.

The reaction times from the "normal" two category judgments were separated into temporal ranges and for each range the percentages correct were calculated. The results (not shown) demonstrated that the performance of the younger subjects was essentially unrelated to reaction time. For the older group there seemed to be a slight decrement in performance with increased reaction time. A similar plot for the "fast" judgments showed no appreciable trend for either group.

A plot of the distribution of response time (t_R) for older and younger (not shown) indicates that a factor of 1.3 applied to the reaction times of the younger makes both distributions essentially identical. This can be graphically illustrated by plotting the cumulative percentage of all individual reaction times for the "fast" situation as a function of 3.1 $\log_{10}(0.77at_R - 0.38)$, where $a = 1$ for older subjects and $a = 1.3$ for younger subjects. The above relation transforms the distribution very nearly into a normalized, error function. When median responses are used, then the transformation, 3.1 $\log_{10}$ $(at_R - 0.8)$, with $a = 1.0$ and 1.4, is satisfactory.

TABLE 5. REACTION TIME.

Test Condition		Younger	Older	O – Y	O/Y
Normal, mean		4.04	4.68	0.64	1.13
Normal	Q_1	1.44	1.90		
	Q_2	2.34	2.88	0.54	1.23
	Q_3	4.10	4.66		
Fast, mean		1.46	2.04	0.58	1.40
Fast	Q_1	1.03	1.28		
	Q_2	1.29	1.74	0.45	1.35
	Q_3	1.97	2.48		
Set Change median		0.70	0.98	0.28	1.40
Set Change (relative to median)		0.30	0.34	0.04	1.13

DISCUSSION

Present results show that older persons have more difficulty in discriminating weight differences than younger subjects. Also, increasing the difference between the standard and comparison weight does not improve discrimination in the elderly as much as in younger subjects. While in general these findings were anticipated, other results were not and deserve comment. The two most striking results which were unanticipated were (a) the lack of cor-

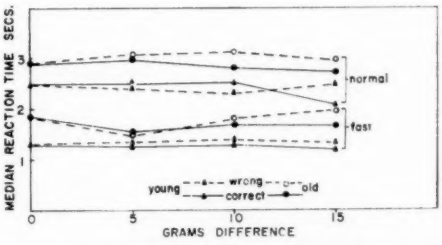

Fig. 3. Age differences in oral response time as a function of the difference in the two weights. Data are presented separately for the normal circumstance and the time pressure, "fast," in which subjects were urged to make their judgments as quickly as possible.

relation between response time and task difficulty for both age groups and (b) the relatively small age difference in "response perseveration."

In every instance the older group was slower than the younger. In neither group, however, was the response speed related to the difficulty of the judgment. From previous work it was expected that the response time would become slower as the task became difficult, i.e., smaller weight differences. Previous studies have shown a close relation between response time and the difficulty of the perceptual task (2, 4, 7). The percentage of correct response and response time do change at different rates as the task is varied in difficulty, yet the present data lie with the difficulty range when response time might be expected to change, e.g., pitch discrimination (5). While it is not possible to explain the absence of this expected relationship, several factors may be relevant. It may not have been possible, under the conditions of the study, for the subject to use a longer time to improve his judgments. Also, the relationship may be susceptible to context or set influences.

Distinctions were made in this paper between several kinds of response determinants in the subjects: acceptance of equality of stimuli, bias or preference for the right or left hand, perseveration or the dependency of a subsequent judgment upon a previous one either due to an effect of the response *per se* or to a common basis in a fluctuating ability to discriminate. No striking age difference was found in the acceptance of equality, nor was an age difference in hand bias found. The analysis of perseveration did show increased perseveration for the older group, both "response" and "fluctuating" threshold types. This latter point is of considerable interest since it suggests that some aspects of perseveration of response with age are not independent of the threshold to discriminate. The effects of increased complexity of judgment upon the responses of old and young subjects has yet to be explored (11).

SUMMARY

The effects of age upon discrimination of lifted weights was studied by comparing data obtained from 39 younger subjects, median age 24 years, and 42 elderly subjects, median age 74.

Subjects were required to distinguish a standard weight of 100 Gm. from a variable weight; 100, 105, 110, or 115 Gm. Ten different series of judgments were examined in which the conditions were systematically varied, such as, simultaneous right and left hand discrimination, successive presentations of stimuli to same hand, 2 or 10 sec. delay between first and second weights in a pair, judgment time limited and time unlimited, use or non use of "equal" judgment category, and a regular versus random series of weight gradations. Response time was recorded under certain of the conditions.

In simultaneous discrimination, weight presented to right and left hands, the relative performance of elderly to young persons was about 70% for normal speed, and 60% under "speed" conditions. There was a significant correlation in both age groups between performance when told to respond as fast as possible and when given a short time for judgment.

In successive discrimination the elderly subjects did nearly as well (about 93%) as the younger subjects. Delay of judgment from 2 to 10 sec. was without effect in either group.

Older subjects showed more perseveration in the sense that an effect of a judgment had a residual effect upon the next judgment. This effect was not so much a "perseveration of response" as it was a persistence or perseveration of a bias which originated as a spontaneous fluctuation of the ability to discriminate. Thus, some aspects of perseveration may not be independent of the threshold to discriminate. A method for distinguishing the types of perseveration is described.

In all instances the response time of the older subjects was slower than the younger: the younger group was on the average 0.5 sec. faster. Neither group, however, showed a relation between response time and task difficulty, the latter being defined as the weight difference being discriminated.

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THE EFFECT OF AGE ON TASTE SENSITIVITY

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This paper is concerned with studying the developmental changes which occur in sensitivity to the 4 primary taste qualities viz. sweet, sour, salty, and bitter. Previous research on the effect of age on taste sensitivity has been quite meager in relation to other sense modalities. Almost all of it is concerned with the neonatal or prenatal periods. This literature has been reviewed by Pratt (10). What little research has been done on the later age periods has been confined to the sense of bitter (5, 13) and sweet (11).

The research on the effects of later age changes on sensitivity to bitter has been wholly restricted to the use of the "bitter-tasting" chemical phenyl thiourea (PTC), the so-called "taste blindness" substance (13). The results are anything but clear. Harris and Kalmus (5), for example, report that sensitivity to PTC decreases by approximately a factor of two for each 20 years of age. Cohen and Ogden (4), on the other hand, in a review article cite several studies which fail to confirm such findings. These conflicting results, it has been suggested (9), may reflect the unusual nature of PTC or its use in unpurified form. The only study on sensitivity to sweet has been performed by Richter and Campbell (11). They found that subjects between the ages of 52 and 85 had sucrose taste thresholds almost three times as great as those of young subjects of ages 15 to 19 years.

The purpose of the present study is to investigate not only the effect of age on sensitivity to sweet and bitter, using less controversial substances, but also sensitivity to substances of a salty and sour nature.

METHOD

Materials. The substances used in the experiment to produce the sweet, salty, sour, and bitter tastes were respectively, sucrose, salt (NaCl), hydrochloric acid and quinine sulphate. The test stimuli consisted of 18 different concentrations for sweet ranging from .015% to 2.000%, 20 for salt ranging from .005% to 2.000%, 17 for sour ranging from .0003% to .0270%, and 23 for bitter ranging from .000003% to .002000%. Each step in a series was a multiple of .75 of the preceding step. Distilled water was used, for comparative purposes, throughout the experiment.

Subjects. One hundred subjects were used in the experiment. The sample was made up of 25 individuals aged 15 to 29, 16 aged 30 to 44, 23 aged 45 to 59, 27 aged 60 to 74, and 9 aged 75 to 89. Twenty of these were females. Fifty-eight of the group were smokers. The subjects over the age of 60 were drawn largely from a senior citizens club while the remainder were drawn from university undergraduates and staff.

Procedure. The subjects were blindfolded and presented with two 20 cc. beakers, one containing distilled water and the other a "taste" solution of very low concentration. They were required to taste the two liquids by sipping from the beakers as often as they wished. The concentration of one solution was then gradually increased until the subject reported that it tasted different from the other (the distilled water). This value was called a difference threshold. The concentration was then further increased until the subject reported a definite taste quality, e.g., bitter. This value was called a taste threshold. The subjects were given three trials on each of the 4 stimulus series. At the beginning of each series the subjects were told which taste quality to look for, e.g., whether sweet, salty, sour, or bitter. Short rest intervals of a few minutes duration were interspersed between the different trials of a particular series. The mouth was thoroughly rinsed before the next taste substance was used. All subjects who were smokers were asked to refrain from smoking for at least one hour prior to testing.

RESULTS

Over-all taste sensitivity. Figure 1 summarizes the course of developent and decline of over-all taste sensitivity (mean of 4 taste thresholds expressed in standard scores). It can

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be seen that taste sensitivity remains unimpaired until the late fifties, after which it shows a sharp decline. An F test applied to the means of the 5 age groups is significant at the .001 level ($F = 9.223$). The apparently greater sensitivity of the 30-44 age group over the 15-19 and 45-59 age groups is not statistically significant ($t = .985$, $p > .05$).

Sensitivity to specific taste qualities. Figure 2 and table 1 summarize the relationship between age and sensitivity to the 4 primary taste qualities. It can be seen that the course of development and decline for sensitivity to sweet, salty, sour, and bitter is essentially the same. All curves show a noticeable decline after the late fifties. Certain differences appear in the oldest group (75-89) but since only 9 cases were tested in this age category, little reliance can be placed on these results. Table 1 shows significant F ratios for effect of age on sensitivity to sweet, salty, and bitter. The F ratio for sour is not significant, although its curve is similar in shape to the others. However, when the mean threshold of the 36 subjects over the age of 60 is compared with that of the 64 subjects below this age it is found to be significantly different ($t = 2.319$, $p > .01 < .05$). This would seem to suggest that a significant decrement in sour sensitivity does occur in the later years of life.

Difference thresholds. In addition to taste thresholds, measurements were also made of difference thresholds. These are summarized in table 2. It can be seen that the difference thresholds show essentially the same age trend as do the taste thresholds. There are certain differences between the two in the oldest age group (75-89) but since only a small sample was used in this category, little significance can be attached to them.

Effect of sex and smoking. Taste thresholds of 20 females matched with 20 males for age and smoking failed to reveal significant differences at the .05 level for either over-all taste sensitivity or for the specific taste primaries. Snedecor's F test for disproportionate subclass numbers (12) was also used to evaluate the differences between the 58 smokers and 42 non-

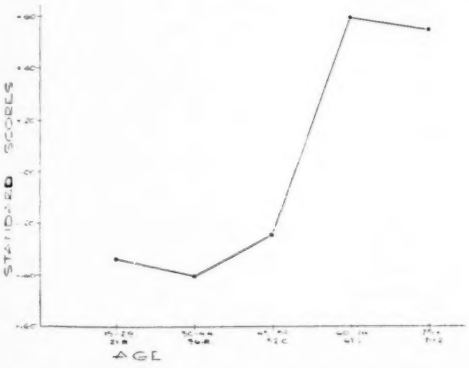

Fig. 1. Relationship between age and taste sensitivity (composite of 4 taste qualities). Below each age interval is given the mean age of subjects in that interval.

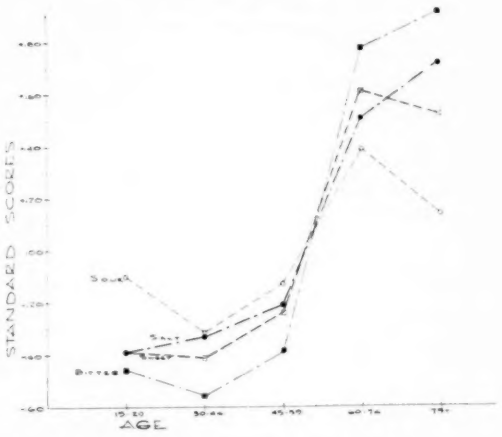

Fig. 2. Relationship between age and sensitivity to substances of a sweet, sour, salty, and bitter nature.

TABLE 1. TASTE THRESHOLD VALUES IN PERCENTAGE CONCENTRATIONS FOR THE FOUR TASTE QUALITIES.

Age Group	15-29	30-44	45-59	60-74	75-89	F
N	25	16	23	27	9	
Sweet	0.540	0.522	0.604	0.979	0.914	6.142*
Salty	0.071	0.091	0.110	0.270	0.310	6.827*
Sour	0.0022	0.0017	0.0021	0.0030	0.0024	1.618
Bitter	0.000321	0.000267	0.000389	0.000872	0.000930	7.540*

* Significant at .001 level.

TABLE 2. DIFFERENCE THRESHOLD VALUES IN PERCENTAGE CONCENTRATIONS FOR THE FOUR TASTE QUALITIES.

Age	15-29	30-44	45-59	60-74	75-89
Sweet	0.275	0.268	0.281	0.430	0.396
Salty	0.032	0.036	0.047	0.123	0.101
Sour	0.0012	0.0009	0.0009	0.0026	0.0012
Bitter	0.000176	0.000094	0.000111	0.000623	0.000196

smokers making up the sample. As with the sex variable, no significant differences at the .05 level could be found.

DISCUSSION

The results of the present investigation show quite clearly that the course of development and decline of taste sensitivity for the 4 taste primaries, viz., sweet, sour, salty, and bitter is essentially the same for each. All show a noticeable decline after the late fifties. There is some suggestion, however, that sensitivity to sour is less affected by age than the other taste qualities. The results on sweet are supported by those of Richter and Campbell (11), who found that the sucrose taste thresholds of subjects over the age of 50 are much higher than those of young adults. Furthermore, the results on sensitivity to bitter are supported by some of the studies using the "bitter tasting" substance PTC (5, 13).

The finding that taste sensitivity begins to decline quite late, after the late fifties, is in line with certain results obtained on other sense modalities. For example, Misiak (7), studying the relationship between age and critical flicker frequency, reports that only after the age of 55 is the decline statistically significant. Birren, Bick, and Fox, (3) working on dark adaptation, report that only after the age of 50 is the decline noticeable and after 60 that it is pronounced. Similarly. for vibratory sensitivity, the decline begins in the late fifties (8). Thus the later age changes in taste sensitivity conform to those occurring in some of the other sense modalities.

The decreasing sensitivity to taste with age is probably due to certain degenerative changes occurring in the taste receptors. Three anatomical studies indicate that such changes do occur. Allara (1) reports that the gustatory papillae reach full development at puberty and that regressive changes set in after the age of 45. Furthermore, both Machizuki (6), studying the foliate papillae, and Arey, Tremain, and Monzingo (2) the circumvallate papillae, report a decrease in number of papillae with age. In addition to a decrease in number of papillae there is also a decrease in number of taste buds. Arey and associates report that in young adults there are approximately 250 taste buds in each circumvallate papilla; over the age of 70 there are less than 100. These anatomical changes are undoubtedly largely responsible for the decreased taste sensitivity with age.

SUMMARY

A sipping technique was used to test 100 subjects, aged 15 to 89, for taste sensitivity to substances of a sweet, sour, salty, and bitter nature. It was found that the curve of development and decline for sensitivity to each of the 4 taste primaries was essentially the same. All curves showed a noticeable decline after the late fifties. No sex differences were observed nor were there any differences in taste sensitivity between smokers and non-smokers.

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GERIATRIC PRACTICE

HEART DISEASES IN OLD AGE

I. SYMPTOMATOLOGY AND DIAGNOSTIC PROCEDURES

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It is a well-known fact that diseases of the heart are among the most common diseases occurring in old age and often constitute the immediate cause of death. The most frequent cause of heart disease in this age group is atheromatosis of the coronary arteries and their branches with subsequent thrombus formation and interruption of the arterial blood supply. The second most frequent condition responsible for the development of heart disease is arterial hypertension. A third cause of heart disease which occurs not infrequently is disturbances of the pulmonary circulation leading to chronic cor pulmonale. Other factors in the pathogenesis of heart disease are metabolic disturbances, particularly diseases of the thyroid gland, diabetes mellitus, and obesity. Valvular heart disease, especially of rheumatic etiology, is relatively infrequent in the senium.

The strictly senile changes of the heart only rarely lead to cardiac failure. In aged persons who do not suffer from marked coronary sclerosis or hypertension an atrophic condition of the heart usually develops. The myocardial fibers decrease in number and a deposition of brown pigment takes place, which causes the myocardium to asssume a brown color (atrophia fusca cordis). These changes are more pronounced in women than in men, and they occur especially in persons who are underweight, inactive, and suffer from debility requiring prolonged confinement to bed.

EXAMINATION OF THE HEART

Physical examination. The estimation of the heart size in old persons through palpation and percussion is frequently not possible. The existence of senile pulmonary emphysema makes it impossible to define the point of maximum impulse. For the same reason an evaluation of the borders of the heart through percussion is usually unreliable. The roentgenological examination of the heart is therefore of special importance when dealing with aged patients.

Auscultation of the heart in old subjects reveals murmurs in about one-third to one-half the individuals; the murmurs are usually of a blowing, shrill, or rough systolic character. Such murmurs, however, are not due to ordinary valvular disease, but are in the majority of the cases caused by an age-associated stiffness of the valves, with calcification of the valves themselves, or the valvular annuli. Thus a rough systolic murmur is frequently heard over the aortic area in the absence of aortic stenosis. The calcification of the annulus of the mitral ostium constitutes a geriatric disease entity; in this condition a rough systolic murmur is heard over the apical region or at the left sternal border. A brief, late-diastolic rumbling murmur occasionally precedes the systolic murmur and is in that case acccompanied by a moderate thrill. Because many elderly persons, as mentioned above, suffer from pulmonary emphysema the heart sounds or murmurs frequently become indistinguishable or very weak. These facts do not of course permit the assumption that the patients are suffering from cardiac weakness.

X-ray examination of the heart. The roentgenological examination of the heart is of the greatest importance for the cardiac diagnosis. A slight to moderate enlargement of the heart is often encountered in elderly persons who have not shown signs of hypertension or cardiac disease and who have a normal electrocardiogram. The finding of cardiac enlargement usually indicates the existence of coronary sclerosis with myofibrosis or the scar of a myocardial infarction, which have resulted in cardiac hypertrophy and dilatation. The roentgenological

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examination of the heart is also of distinct value in the diagnosis of valvular disease (aortic stenosis, mitral valvular disease), cardiac enlargement due to hypertension, cor pulmonale, and metabolic diseases (especially diseases of the thyroid). The routine antero-posterior examination must often be supplemented by lateral and oblique exposures. These latter types of roentgenograms are of particular importance in the diagnosis of cor pulmonale, congenital heart disease, mitral valvular disease (including calcification of the mitral annulus fibrosus), and aortic aneurysm.

Electrocardiography. The electrocardiograms of persons over 60 years will generally show pathological changes to a greater or lesser degree as an expression of myocardial lesions (scars following myocardial infarction, myofibrosis). It is, however, by no means unusual to encounter a completely normal electrocardiogram in an individual in whom serious myocardial damage is found at autopsy. Such "silent" zones are found especially in the interventricular septum and in the section of the heart which forms the obtuse margin. On the other hand, one will frequently observe the absence of macroscopic pathological changes at autopsy in subjects who had exhibited abnormal electrocardiograms (auricular fibrillation, sino-auricular and atrio-ventricular block, bundle branch block, inverted T-waves in first and second leads).

The changes in the electrocardiograms which are the results of the aging processes themselves include: 1) flattening of the P-waves, 2) slight prolongation of the PQ, QRS, and ST intervals, 3) enlargement of the R-waves in the first lead associated with an increased axis deviation to the left, 4) reduced initial and terminal complexes, and 5) increased tendency to knot formation and slurring of the initial complex. In the precordial leads an increased incidence of a Q-wave in the V_3 lead and a depression of the ST interval in leads $V_{4\text{-}6}$ are found. It should be mentioned that an axis deviation to the right is found in aged persons of asthenic body type. If, however, the patient is not of the asthenic type an axis deviation to the right must be considered as pathological, indicating an increased load on the right side of the heart (with suspicion of mitral valvular disease or cor pulmonale).

The presence of inverted T-waves in the first and second leads is comparatively common in the senium and must be considered as definite evidence of myocardial damage (sequels of anterior myocardial infarction, hypertensive heart disease, myxedematous heart, etc.). A deep Q_3-wave may be an expression of occlusion of the right coronary artery with posterior wall infarction, simple coronary sclerosis, or cor pulmonale, but in obese patients with a high diaphragm and subsequent transverse position of the heart a deep Q_3-wave may also be found. The value of the unipolar precordial leads ($V_{1\text{-}6}$) is considerable in the field of geriatric medicine. The first infarctions in elderly persons are usually small and located in the lateral part of the anterior wall of the heart where the electrocardiographic changes are expressed only through an inversion of the T-waves in leads $V_{4\text{-}6}$.

CARDIAC ARRHYTHMIAS AND CONDUCTION ANOMALIES

Cardiac arrhythmias and conduction anomalies occur very frequently in elderly persons. Thus extrasystoles may be observed in the majority of such persons if they are subjected to frequent physical examinations. In contrast to young persons the presence of extrasystoles in elderly subjects is rarely associated with subjective symptoms and may not even be noticed. In general, too great significance should not be attached to this type of arrhythmia; only in those cases where several extrasystoles occur in uninterrupted sequence and where the electrocardiogram shows various origins for the extrasystoles is there reason to suspect the existence of myocardial damage. A number of drugs (digitalis, epinephrine, ephedrine, amphetamine) which are known to be able to produce extrasystoles seem to possess this ability to an even greater extent in elderly subjects. *Sinus arrhythmia* occurs rarely in the senium; thus pronounced cases of respiratory arrhythmia are practically never seen. On the other hand, a type of sinus arrhythmia which is completely independent of the respiratory phases is occasionally encountered; this arrhythmia (pseudoarrythmia perpetua) may by palpation of the pulse and by auscultation be mistaken for true perpetual arrhythmia caused by auricular fibrillation and auricular flutter with irregular blocking. The *auricular fibrillation* is a frequent type of arrhythmia in aged persons; the incidence of this condition among hospitalized elderly patients is about 10%. The etiology of the arrhythmia is chiefly hyperten-

sion and coronary sclerosis with myocardial damage, less frequently thyrotoxicosis, and only rarely mitral stenosis. Coronary occlusion and sudden cardiac decompensation are also capable of eliciting auricular fibrillation. In elderly persons the auricular fibrillation is usually associated with a comparatively slow ventricular rate, namely from 70-90, although higher rates are also seen. Auricular fibrillation occurs not infrequently in the form of paroxystic attacks, for instance following coronary occlusion. It is the rule, however, that the paroxystic attacks of auricular fibrillation sooner or later proceed to a condition of permanent auricular fibrillation. In very rare instances the auricular fibrillation is accompanied by a complete atrioventricular block (fig. 1). This may be the result of overdosing with digitalis in a patient with auricular fibrillation; the patient in that case may show a regular, slow pulse and heart rate of about 40, at the same time as the P-waves are not visible in the electrocardiogram. The prognosis of auricular fibrillation in the senium is comparatively good. Many patients are capable of living with this type of arrhythmia for 10-15 years, at least if it is not associated with rapid ventricular rate. The decisive factor under these circumstances is not the arrhythmia itself, but the condition of the coronary arteries and the myocardium. *Auricular flutter* is encountered very rarely in the senium and, if present, occurs nearly always in the paroxystic form. It proceeds relatively quickly to a condition of fibrillation-flutter and subsequently to pure auricular fibrillation.

Among the conduction anomalies in the senium the *atrio-ventricular block* is the most common. In elderly persons the atrio-ventricular conduction time increases toward the upper limit of normal (0.21 second), and slightly increased values are not at all rare in persons with otherwise normal cardiac condition. Partial and complete atrio-ventricular block are also seen rather frequently in geriatric hospital departments. The prognosis seems to be favorable, provided the patients can limit their activities. Among the *intraventricular* conduction anomalies the most common type is the Wilson-Bayley block, but the classical left bundle branch block is also encountered frequently. The prognosis seems to be the same for the two types of block, and a survival time of 10 years or more after the diagnosis of the conduction anomaly has been established is not unusual. But here also the underlying heart disease will be the decisive factor. Among conduction anomalies which occur less frequently in the senium may be mentioned combined sino-auricular and atrio-ventricular block, combined atrio-ventricular and intraventricular block, intermittent bundle branch block, and alternating bundle branch block. The two latter types constitute incidental electrocardiographic findings and are chiefly of scientific interest. Digitalis seems to be the eliciting factor in persons who already suffer from latent conduction disturbances.

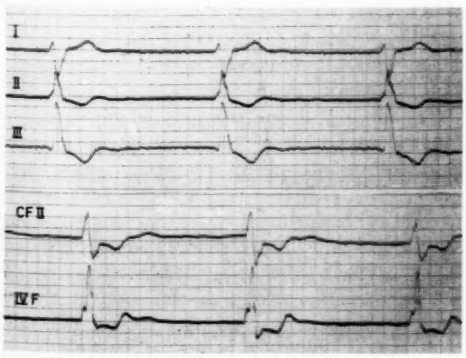

Fig. 1. Electrocardiogram showing auricular fibrillation, complete atrioventricular block, and right bundle branch block (De Gamles By, Copenhagen).

ATHEROSCLEROTIC HEART DISEASE

The atherosclerotic heart diseases manifest themselves in different ways. Changes in the intima of the coronary arteries will lead to ischemia in several small areas of the myocardium when the finer branches of the arteries are involved. Such ischemia causes small disseminated necroses, and, after scar formation, the picture of diffuse myofibrosis develops. Clinically these changes often reveal themselves through an enlargement of the heart, and, in severe instances, through cardiac decompensation.

The atheromatous changes occur, however, usually in the main coronary arteries and their larger branches, especially at the sites of division. As the result of the atheromatous changes in the intima (consisting first of cholesterol and later of calcium deposits, possibly in connection with mural fibrin accumulations) the arterial lumen is narrowed, which gives rise to ischemia under conditions where there is an

increased demand for blood supply as in physical activity. Psychological disturbances which produce spasms in sections of the coronary arteries that are not yet the site of arteriosclerosis act in a similar way.

The occurrence of classical angina pectoris is usually less frequent in the senium because most elderly persons are engaged in only moderate physical activity and generally avoid exposure to cold and windy weather. Simple angina pectoris is therefore not a predominant symptom among elderly subjects admitted to hospitals, custodial institutions, or old age homes.

An inadequate coronary circulation, caused by atheromatosis or previous thrombus formation, may be further impaired as the result of large blood losses or other conditions of anemia, or through shock occurring in connection with the use of hypotensive drugs. As the result of the insufficiency of the coronary circulation prolonged episodes of cardiac pain develop, and if the ischemia is not quickly remedied smaller or larger myocardial infarctions will form. The differential diagnosis between coronary insufficiency and coronary occlusion is often difficult.

Coronary occlusion is one of the most frequent diseases of the senium. The cause of the occlusion is in practically all the cases a thrombosis of the coronary artery, whereas embolization of a coronary artery must be considered as extremely rare. Persons of the pycnic, plethoric body type are predisposed to be the victims of coronary thrombosis. Among the individuals of this "thrombophilic" group the incidence of obesity, diabetes mellitus, and gout is extremely high. Hypercholesterolemia and reduced coagulation time are other frequent findings in these subjects.

The incidence of coronary occlusion increases with age, and the disease occurs earlier in men than in women. In geriatric wards acute coronary occlusion is encountered in about 5% of the patients. The largest absolute number of cases of coronary thrombosis occur in the fifth and sixth decades, and only 2% before the age of 40 years. Such early cases are chiefly seen in patients suffering from hereditary hypercholesterolemia (hereditary xanthomatosis). In approximately one-half of the cases of coronary occlusion the patients have previously presented signs of coronary sclerosis over a shorter or longer period, whereas in the other half of the subjects the coronary occlusion occurs as the first symptom of the disease.

The attack of coronary occlusion itself may take place suddenly, without any warnings, but is often preceded by a period lasting from a few hours to several weeks characterized by moderate attacks of precordial pain or oppression. The attack usually occurs spontaneously, but may be elicited by a trauma, a psychological episode associated with coronary spasm, an infection, treatment with serum or vaccine, surgery, or treatment with various drugs, particularly of the type which produce hypotension. Under these circumstances the thrombus formation may be the result of traumatic or chemical damage of the already atheromatous coronary vascular wall in combination with an increase in the coagulability of the blood.

With regard to the clinical symptoms associated with coronary occlusion the severe *precordial pain* which occurs in about one-half of middle-aged patients is not as pronounced in the senium. This may be due to the fact that many elderly persons are more torpid in their reactions and that patients suffering from senile dementia usually are unable to give adequate information. In the case of small thromboses the condition may pass without any symptoms, or with only few symptoms. This contention is supported by the fact that infarction scars connected with coronary occlusion frequently are found at autopsy in old subjects who have had unequivocal clinical symptoms of the disease. Pathological-anatomical studies show on the whole that coronary thromboses and myocardial infarctions occur much more frequently than is generally assumed, especially in elderly individuals. For this reason every attack of angina pectoris which lasts more than a few minutes should arouse suspicion of coronary occlusion. The same applies to attacks occurring during a state of inactivity.

The *drop in blood pressure* which generally follows an attack of coronary occlusion with myocardial infarction is usually more pronounced in elderly patients, both with regard to degree and duration. This fact must be ascribed to two factors, namely the aggravation of a previously existing cardiac insufficiency and the decreased elasticity of the arterial system caused by atheromatosis and medial sclerosis. The fall in blood pressure is frequently so marked that a state of collapse sets in with blood pressure values considerably below 100 mm. Hg. This condition is very dangerous and

is undoubtedly responsible for the fact that a large proportion of elderly patients with coronary thrombosis die during the acute stage of the disease. Only a quick intervention with dropwise infusion of norepinephrine may save these patients.

Signs of cardiac insufficiency occur more frequently in elderly than in middle-aged patients, because the former usually have suffered previous attacks of coronary thrombosis, or because the old subjects already suffer from diffuse myofibrosis and a damaged myocardium. The symptoms of cardiac insufficiency may become evident immediately after the occurrence of the occlusion, but frequently develop gradually as the myocardial infarction is converted to scar tissue, or when the patient during convalescence is exposed to physical strain. The symptoms of insufficiency may be dominant among the clinical features of coronary thrombosis and may to some extent distort the classical picture of the disease. It is therefore easy to mistake the condition for cardiac insufficiency of other etiology, for instance valvular disease, cor pulmonale, and hypertensive heart disease; similarly, differential diagnostic problems may emerge in case of pulmonary disease, especially embolism or thrombosis of the pulmonary artery. The so-called *pulmonary type* of coronary thrombosis must therefore always be kept in mind in the practice of geriatrics. In patients suffering from marked cerebral arteriosclerosis the failing heart function may cause cerebral anoxia with disorientation and confusion *(cerebral type)*. Furthermore, the acute attack of coronary thrombosis may be associated with severe vomiting and diarrhea, which, in connection with the often deep-seated pains, produce a clinical picture closely resembling that of acute gastro-enteritis *(gastrointestinal type)*. A special subcategory of coronary occlusion with cardiac infarction is finally composed of those cases leading to *rupture of the heart*, hemopericardium, and death. Rupture of the heart occurs with significantly greater frequency in old than in middle-aged persons, because it is the larger coronary branches which are the site of thrombosis in elderly subjects and because of frequent preexisting scars of infarction and myofibrosis.

The temperature elevation which accompanies the acute coronary occlusion and infarction formation is often less pronounced than in middle-aged persons. Even in the presence of large infarction fever may be absent. If the fever persists longer than one week a new thrombus formation or pulmonary embolism or thrombosis should be considered.

The leucocytosis which generally occurs in connection with larger myocardial infarctions is not as pronounced in old as in middle-aged patients. The same pertains to elevation of the sedimentation rate. Besides, it should be recalled that a large number of elderly persons already have an elevated erythrocyte sedimentation rate because of other diseases: chronic cholecystitis, chronic urinary infection with or without renal complications, sigmoiditis, polyarthritis, etc. For this reason, if a determination of the sedimentation rate before the episode of the coronary attack is not available, the first test has little value. Only if repeated sedimentation rate measurements show an increase in the values does the test have diagnostic significance.

The recent introduction in the clinical laboratory technique of a procedure for determination of the *serum transaminase* (serum glutamic acid-oxalacetic acid transaminase, or serum GOT) has proved to be of the greatest value also in geriatric medicine. This test constitutes a definite clinical advancement in the handling of elderly patients with coronary thrombosis because these patients frequently display atypical symptoms. The increase in the transaminase values takes place a few hours after the occlusion and infarction and reaches a maximum in 24 or 48 hours. After one week the value has returned to normal. The increase in the transaminase value is roughly proportional to the size of the infarction. In the case of small, lateral infarctions which occur during the early stages of coronary disease the increase in the serum transaminase level is only slight.

Differential diagnosis: The differential diagnosis between coronary thrombosis and *acute abdominal disease* (cholelithiasis, gastric or duodenal ulcer) may be difficult. The pain associated with acute coronary occlusion is generally deep-seated and located in the upper part of the epigastrium; furthermore, irradiation of the pain to the arms may not occur. The condition of shock associated with perforated gastric ulcer may erroneously be diagnosed as cardiac shock. The case history in these patients providing information about previous attacks of pain with jaundice, dark urine and light-colored stool, or typical ulcer

symptoms, is of considerable importance. The electrocardiogram with precordial leads, especially when repeated at intervals of hours and days, and the serum transaminase determination are usually of decisive significance under these circumstances. The differential diagnosis between coronary thrombosis and the above-mentioned abdominal disease is of particular importance, because the conductance of an exploratory laparotomy in a patient with coronary occlusion constitutes one of the gravest errors. Such patients only in rare instances survive the surgery.

Another disease which can cause serious differential diagnostic problems is *thrombosis or embolism of the pulmonary artery.* In elderly persons phlebitis in the extremities or in the pelvis is often overlooked, and the patient's serious condition with chest pain, dyspnoea, tachycardia, and falling blood pressure may simulate coronary occlusion. The demonstration of a pulmonary infarction through auscultation, in connection with X-ray examination of the chest, one or several electrocardiograms, and determination of the serum transaminase value, will usually provide the diagnosis. Furthermore, the temperature curve will prove characteristic: In coronary occlusion with myocardial infarction the temperature will return to normal in a few days or a week, whereas in pulmonary embolism or infarction the temperature will fluctuate over long periods of time and the fever will not respond to antibiotics, in contrast to the condition in pneumonia.

HYPERTENSIVE HEART DISEASE

Hypertensive heart disease is a frequent finding in the senium, but the condition is rarely an uncomplicated one, since it is generally associated with coronary sclerosis and subsequent myocardial damage. The *malignant type of hypertension* must be designated as rare in the senium, whereas *essential hypertension* is rather frequent. The most common type of hypertension is, however, *simple systolic hypertension,* in which disease the systolic blood pressure is moderately elevated, whereas the diastolic blood pressure is within normal limits.

The *simple systolic hypertension* usually does not cause any increased load on the heart. For this reason hypertrophy of the left ventricle is often lacking in spite of many years' duration of the disease; similarly, the electrocardiogram does not show left-sided axis deviation. In contrast to this, *essential hypertension* with increased systolic and diastolic blood pressure values causes increasing cardiac hypertrophy with typical changes in the heart contours and prominence of the aortic arch. The electrocardiogram shows increasing left-sided axis deviation and gradual changes of the T-wave in the first lead, namely flattening of the T-wave, which subsequently becomes isoelectric or diphasic and finally becomes inverted. The changes of the T-wave are indicative of myocardial damage; through treatment of the hypertension at an early stage the inversion of the T-wave may return to normal.

The time at which the essential hypertension will produce subjective and objective cardiac changes depends on the level of the blood pressure, particularly of the diastolic pressure, the duration of the hypertension, the extent to which the subject is exposed to physical stress, and the condition of the coronary arteries and the myocardium, particularly the presence of previous coronary occlusion and myofibrosis.

The first manifest symptoms of hypertension are dyspnoea on exertion and palpitations. At a later stage sensation of oppression and attacks of precordial pain occur. With increasing coronary sclerosis, cardiac hypertrophy and dilatation and myocardial degeneration left-sided heart failure and symptoms of manifest cardiac insufficiency set in (dyspnoea at rest, cardiac asthma, pulmonary congestion, Cheyne-Stokes' respiration). The condition is subsequently complicated by right-sided heart failure with symptoms due to stasis in the venous system. In evaluation of the seriousness of the condition the extent of the eye ground changes, the changes in renal function, and the findings on roentgenological examination, electrocardiography and cardiac function tests are of importance.

COR PULMONALE

Because pulmonary embolism and pulmonary thrombosis occur often in elderly subjects, especially in persons who are completely or nearly completely confined to bed, the condition of *acute cor pulmonale* is encountered not infrequently in such individuals.

The clinical symptoms consist of a sensation of oppression, dyspnoea, cyanosis, perspiration, and rapid, weak, and often somewhat irregular pulse. With a waning of the strength of the patient a soporous condition supervenes, and

the patient dies exhibiting signs of increasing cardiac insufficiency (stasis of the veins of the neck and stasis of the liver). Examination of the heart reveals extension of the cardiac dullness to the right, a systolic murmur in the second left intercostal space, accentuation of the second pulmonary sound, and, occasionally, a diastolic gallop rhythm. The electrocardiogram shows right-sided axis deviation, deep S_1, inversion of T_3 (and occasionally of T_2) together with depression of the RS-T_1 interval, elevation of the RS-T_3 interval, and a large Q_3-wave. The electrocardiogram thus to a large extent resembles that found in posterior myocardial infarction. The deep S_1-wave, however, supports the diagnosis of pulmonary embolism. Furthermore, the electrocardiographic changes in pulmonary embolism are of a more transient character and usually persist for only a few days in contradistinction to posterior myocardial infarction in which condition the changes remain for a longer time. In the differential diagnosis between cor pulmonale and coronary occlusion with posterior infarction a history of previous episodes of phlebitis will of course support the diagnosis of pulmonary embolism.

Of definitely greater clinical importance is the condition of *chronic cor pulmonale*, which is a frequent disease in elderly individuals, particularly elderly men. The increasing interest exhibited in this disease during the last several years has resulted in a more frequent diagnosis of this condition *in vivo*, whereas formerly it was an unexpected finding at autopsy. The cause of chronic cor pulmonale is believed to be an increased blood pressure in the pulmonary circulatory system, resulting from diseases of the lungs or the pulmonary vessels. Among such diseases may be mentioned large thromboses or embolisms in the pulmonary arteries, severe pulmonary emphysema, fibrous and atrophic pulmonary tissue changes following chronic bronchitis, bronchiectases, chronic pneumonia, severe silicosis and tuberculosis, and extensive pleural adhesions. Other causes include compression of the pulmonary artery by a pulmonary carcinoma and compression of the lungs resulting from severe chest deformities. Finally, chronic cor pulmonale may be caused by a primary endarteritis (so-called primary cor pulmonale) of unknown etiology (related to Bürger's disease) and by luetic vascular disease (Ayerza's disease).

The clinical picture of chronic cor pulmonale is characterized by the slow development of the disease, with a period of several years generally elapsing between the first slight evidence of hypertrophy of the right side of the heart and complete cardiac insufficiency. A marked cyanosis may constitute a comparatively early symptom of the disease; in that case the cyanosis is caused to a greater extent by the pulmonary condition than by the cardiac complications. The same applies to the dyspnoea, which first occurs as dyspnoea on exertion and later as dyspnoea at rest, but it can be stated in general that the dyspnoea is less pronounced than would have been expected from the degree of cyanosis present. During the last stages of the disease stasis develops in the general circulatory system with dilatation of the veins of the neck and enlargement of the liver, and occasionally ascites and edema of the legs. The diagnosis may be difficult during the early stages of the disease, and the condition is therefore frequently overlooked. Information supplied from the case history concerning diseases of the lungs or conditions interfering with the pulmonary circulation is of great importance. The electrocardiogram often assists in the establishment of the diagnosis, the characteristic findings including right-sided axis deviation, deep S_1, diphasic or inverted T_3 (and occasionally T_2), large Q_3, and in the more pronounced cases enlargement of P_2 and P_3. In the medial precordial leads a high R-wave, and in the lateral leads a deep S-wave, is found. Roentgenological examination of the chest may reveal typical findings during the later stages of the disease; these include: 1) dilatation of the right side of the heart, 2) prominent conus pulmonalis, and 3) wide comma-shaped vessel shadows in the hilar regions without accompanying peripheral pulmonary stasis. The presence of severe pulmonary emphysema or marked kyphoscoliosis will, however, frequently obscure the findings.

VALVULAR DISEASE

During the senium valvular diseases are in general less predominant as compared with coronary and myocardial diseases. This is especially true with regard to rheumatic valvular diseases, which constitute only a small percentage of the diagnoses in a group of geriatric hospital patients. This is simply a consequence of the fact that patients with rheumatic heart disease, acquired at a young age, rarely reach

old age. The verrucous mitral lesions which may be found at autopsy in elderly persons must be presumed to have existed for only a few weeks or months and are considered as an expression of the failing resistance of debilitated individuals toward chronic infections, particularly urinary and bile duct infections.

The presence of *simple aortic stenosis* is nevertheless fairly frequent in elderly persons and occurs chiefly in men. Only in a minority of these patients can evidence be obtained from the case history of previous rheumatic infection, and atherosclerosis must therefore be considered as the leading cause. Especially in the presence of Paget's disease is simple aortic stenosis reported to be a comparatively frequent complication. The possibility of aortic stenosis should therefore be considered in the case of elderly men who complain of dizziness and who have exhibited a tendency to fainting. A low systolic blood pressure and the absence of arterial pulsation in the jugular fossa are common findings in this condition. A systolic murmur over the aortic area is missing in about one-half of the patients. Decisive for the diagnosis is the demonstration through X-ray examination of an enlargement of the left ventricle and the change in the shape of the heart characteristic of aortic valvular disease.

A special geriatric disease entity is the *calcification of the annulus fibrosus of the mitral ostium* which occurs with advancing age. Before the calcification becomes manifest microscopic changes in the annulus take place in most elderly persons: the number of cells in the connective tissue decreases, and the tissue becomes coarse and fibrous with poorly defined delimitation toward the surrounding myocardium. At the same time a deposition of small calcified particles occurs; these particles subsequently combine to form macroscopic calcified deposits, and the annulus is finally converted to a dense calcified ring of excessive thickness (fig. 2). Calcification visible to the naked eye (calcificatio annulus fibrosi mitralis) is found at autopsy in 12% of women in the eighth decade, whereas the incidence in men is only about 3%. The constriction of the ostium resulting from the formation of the calcified annulus is, however, only moderate, for which reason manifest stenosis of the mitral valve with dilatation of the left atrium develops only rarely. On the other hand, calcified ramifications from the annulus fibrosus may invade the interventricular septum and through pressure produce atrio-ventricular block and bundle branch block. Furthermore, the calcification of the annulus fibrosus frequently causes endocardial murmurs, creating differential diagnostic problems. In many patients a rough systolic murmur is audible over the apical region; occasionally a late diastolic murmur is also heard, as can be verified through phonocardiography. The diastolic murmur is usually not the expression of a mitral stenosis, but may merely be ascribed to the fact that the blood during its passage from the left atrium to the left ventricle induces vibrations in the stiff, calcified annulus. Although the calcification of the annulus fibrosus must be characterized as a benign condition which does not shorten the life of the subject, its presence may nevertheless, as explained above, lead to diagnostic errors. The diagnosis of the condition is often a tentative one. In antero-posterior X-ray exposures of the chest the calcified annulus is usually obscured by the heart muscle and the presence of blood in the heart. X-ray examination in the left oblique position offers a greater possibility for demonstration of the calcified annulus. Occasionally the calcification is revealed as a purely incidental finding on routine chest X-ray films.

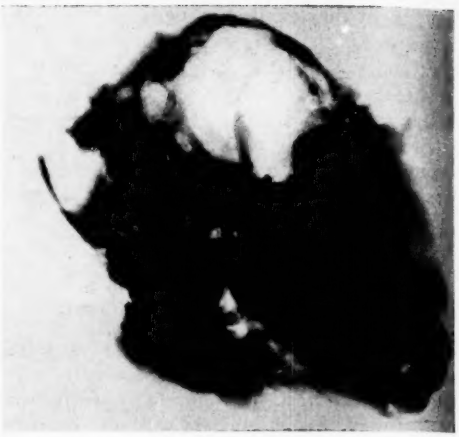

Fig. 2. Marked calcification of mitral annulus fibrosus (roentgenogram of autopsy specimen).

Syphilitic changes of the heart and aorta have during the last decades become much less frequent than previously as the result of the more rational treatment and greater possibility for cure of the disease. *Aortic insufficiency of*

luetic etiology may still occasionally be encountered during the senium, but as a rule patients with syphilitic heart disease fail to reach a high age. The existence of aortic insufficiency will always be suspected if the pulse amplitude is very great as the result of low diastolic blood pressure combined with a normal or slightly elevated systolic pressure. The findings of a typical cardiac murmur (diastolic or systolic-diastolic) over the aortic area, capillary pulsation, and considerable enlargement and dilatation of the left ventricle with the point of maximum impulse in the sixth left intercostal space in the anterior axillary line will confirm the diagnosis. The presence of *luetic aortitis* is found relatively frequently in the senium, being demonstrable in about 2% of autopsies performed on old persons. In contrast to this, *luetic aortic aneurysm* is regarded as a rarity today.

HEART DISEASES ASSOCIATED WITH THYROID DYSFUNCTIONS

The previous contention that *thyrotoxicosis* occurs chiefly in younger subjects has been thoroughly revised after it has been recorded that approximately 30-40% of the cases are encountered after the age of 50 years. The disease in elderly persons reveals itself chiefly through cardiac symptoms; thus auricular fibrillation is found in 25% and cardiac insufficiency in 22% of the patients. When auricular fibrillation is observed in elderly patients the possibility of thyrotoxicosis should be considered, especially in such cases in which the fibrillation cannot be ascribed to hypertension, coronary sclerosis, or mitral valvular disease. The differential diagnosis may be difficult because the classical symptoms of thyrotoxicosis, exophthalmus, thyroid enlargement, and tremor of the hands usually are missing in the senium. Determinations of the basal metabolic rate and of the serum protein-bound iodine level will assist in establishing the diagnosis.

The incidence of *myxedema* in the senium is also greater than is generally assumed. The sluggishness and apathy associated with myxedema are often erroneously interpreted as beginning senile dementia. The possibility of the existence of heart disease due to reduced thyroid function must therefore be considered in the clinical evaluation. The symptoms consist of sensation of oppression and dyspnoea on exertion, but only in the severest cases does manifest cardiac insufficiency develop. Roentgenological examination reveals diffuse enlargement of the heart, and the electrocardiogram often shows isoelectric, diphasic or inverted T-waves in the first and second leads. The presence of a marked sinus bradycardia should always direct the attention to the possibility of hypothyroidism, the diagnosis of this condition being of particular importance because of its response to specific therapy with thyroid preparations. When such treatment nevertheless occasionally proves ineffective the reason for the therapeutic failure may be the existence of atherosclerosis induced by the reduced thyroid function. The diagnosis of myxedematous heart disease is supported by the findings of a low basal metabolic rate and an increased serum cholesterol level.

BOOK REVIEWS

STRIKE BACK AT STROKE, P. H. S. Publication No. 596, U. S. Dept. of H. E. & W., 37 page pamphlet, available from the Supt. of Documents, U. S. Government Printing Office, Washington 25, D. C., 1958, 40 cents.

The purpose of this pamphlet is to give physicians detailed basic information on how to care for a stroke patient at home. It has been reviewed and endorsed by the Committee on Aging, the Committee on Rehabilitation, and the Council on Medical Service of the American Medical Association.

It is a step forward toward giving adequate care to victims of one of the most common and on the other hand one of the most neglected disabilities. It is the firm belief of this reviewer that not enough effort has been made in the past by the medical and related professions to understand and to manage hemiplegia in a rational way. Some of today's well-accepted methods of dealing with stroke patients will probably, in the not too distant future, meet the fate of the bloodletting of years ago.

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REHABILITATION OF THE CARDIOVASCULAR PATIENT, by Paul Dudley White, Howard A. Rusk, Philip R. Lee, and Bryan Williams, McGraw-Hill Book Company, Inc., New York, 1958, 176 pages, $7.00.

This book is divided into eight chapters treating the subjects of cerebral vascular disease, rheumatic heart disease, congenital heart disease, hypertensive heart disease, and coronary artery-myocardial infarction disease.

The most complete section is that on treatment of patients with brain infarction. The other sections are somewhat disappointing. The New York Heart Association functional classification (for employment purposes) is mentioned only, not fully reported. The discussion on mitral commisurotomy does not mention that such patients, if poorly prepared for the new changes in their lives, sometimes are overtly suicidal in the face of brilliantly successful mechanical repair.

This book is clearly not for cardiologists, physiatrists, or medical students. I imagine that it is intended for industrial physicians and general practitioners. I personally do not believe that the philosophical approach toward chronic disease embraced by the authors can be taught in classes or acquired from a book.

Recommended, but not enthusiastically.

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CHOLESTEROL, by David Kritchevsky, John Wiley & Sons Inc., New York, 1958, 291 pages $9.75.

This useful monograph is a handbook on cholesterol, selectively covering the chemical and biological literature in various ways: chronologically, from 1733 to about the middle of 1957; zoologically, from the alpaca to the wooly bear caterpillar; and chemically—in the cholesterol esters, for instance—from acetate to xanthamide. Dr. Kritchevsky has managed to compress all this into less than 300 pages, including a fairly adequate subject index. It seems a monumental work in miniature and is written throughout in an easy style, which guides the reader's attention gently from topic to topic and with occasional hints of dry humor. This book should soon find a place in every biochemical and medical library and in the personal libraries of workers in this field. The 7 chapters are concerned with the chemistry, biosynthesis, absorption, transport, and metabolism of cholesterol, its variation in tissue and blood in different states of health and nutrition, and, finally, with various methods of analysis of cholesterol. An appendix lists physical constants of ca. 300 compounds, physical properties, content in foods, sera, and tissues.

The jacket blurb includes the statement that "the book is not merely a collection of special chapters—but a unified work." It falls considerably short of an ideal unity. It *is*, in effect, a collection of chapters, although a collection between whose parts there has been good communication to minimize overlapping. Each chapter is an independent review. Where there has been inevitable overlapping, as in the chapter on cholesterol in disease with that on blood cholesterol, reference material is repeated with no hint that it has appeared elsewhere. Nowhere is material in any chapter used to throw light on that in another: "Biosynthesis" stands without help from "Chemistry," while the findings in "Blood Cholesterol" are never explicitly modified by those in "Analysis." Viewed in another way, such guidance or correlation as the reader receives is limited by the subject of each chapter. Within a chapter, this guidance is largely implicit in the selection and juxtapositioning by the author of what he regards as the most important data. The reviewer hopes that the undoubted success of this book will encourage the author to bolder interdisciplinary correlations in future editions.

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OLD AGE AND WORK, by Morgens Felbo, Ejnar Munksgaard, Copenhagen, 1958, 236 pages, paper bound, d. kr. 30.30.

The object of this work was to estimate the working capacity of old people from a medical point of view. The island of Bornholm (pop. 49.000) was chosen for the survey. There are a great many reasons why a small sample of this population would have great revelance to the entire number of islanders: infrequency of moving, homogeneity of race, lack of striking economic, cultural, or social change over many years, and frequency of extended work—years in a frugal, non-

industrial economy. The samples consisted of the following, taken by birth date from the National Registry:

	Men	*Women*
Age 65	290	226
Age 70	262	196

These old people were examined in their homes by one or other of two examiners, and by both examiners in the hospital at Rønne.

Classifications investigated were:

Medical. Muscular strength, mobility and contractures; fractures, dislocations, old infections and other disorders of bones and joints; vascular diseases; nervous system; skin.

Economic and Vocational. Breakdown by life work, by geopraphic distribution and by sex and civil status (married, single, widowed, divorced).

Work Capacity. This turned out to be an estimate based on a composite of all previous data.

Results. This is a solid and reliable basic study, nonetheless valuable for the fact that many of the conclusions could have been guessed in advance: old men are stronger than old women; 65-year-old men are stronger than 70-year-olds; right-handed persons do better with the right hand. But there are a few surprises: increased body height correlates with increased strength; with few exceptions obesity correlates with increased strength; persons in heavy manual labor have less strength than other occupational groups.

Because of its over-all excellence some persons may have regrets that this work did not include something on nutrition, endocrine factors, and possibly other data. And of course one may not apply the results to a population of Puerto Ricans or Japanese. A substantial source book in gerontology.

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NEUROLOGICAL BASIS OF BEHAVIOUR, edited by G. E. W. Wolstenholme and Cecilia M. O'Connor, Ciba Foundation Symposium, Little, Brown & Company, Boston, 1958, 400 pages, $9.00.

This volume contains the proceedings of a symposium held at the Ciba Foundation, London, in the summer of 1957, to commemorate the 100th birthday of Charles Sherrington. It is a distinguished volume by distinguished scientists. Its purpose was to review the biological bases of behavior as revealed by current neurophysiological, anatomical, biochemical, psychological, and pharmacological research. The chairman also suggested in his opening remarks that there were "practical" implications as well, . . . "from the utilitarian point of view, it may be pointed out that the future of psychiatry seems likely to be closely linked with the development of this new field of science which attempts to place psychology on a basis of neurophysiology." The scope and currency of the data make it impossible to review the volume as a whole: 19 papers were presented on topics ranging from "The Behavior of Nerve Cells" to "The Relevance of Some Neurophysiological Data to Behavior Disorders." The discussions following the original presentations are also included. The participants were primarily interested in the elucidation of patterns of behavior elicited under a variety of experimental conditions. Thus for someone keenly interested in aging there is not much of direct interest in this volume other than the provocative report of Rosenzweig, Krech, and Bennett that in rat brain cortex, cholinesterase activity declines after a maximum around 100 days. However, since there is often a dual interest in "explaining" aging and "explaining" behavior there are many points in the book which will provoke experiments for the student of behavior and aging.

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BOOKS RECEIVED

Breast Cancer, edited by Albert Segaloff, C. V. Mosby Co., St. Louis, 1958, 257 pages, $5.00.

Cardiovascular Diseases in the U. S. Facts and Figures, American Heart Association, 44 East 23 St., New York, 1958, 15-page pamphlet.

Cerebral Vascular Disease. Transaction of the 2nd Conference Held Under the Auspices of the American Heart Association, Princeton, New Jersey, January 16-18, 1957, Irving S. Wright, Chairman, Clark H. Millikan, Editor, Grune & Stratton, New York, 1958, 224 pages, $4.00.

Cholesterol, by David Kritchevsky, John Wiley & Sons, Inc., New York, 1958, 291 pages, $9.75 (reviewed in this issue, page 00).

Dietary Prevention and Treatment of Heart Disease, by John W. Gofman, Alex V. Nichols, and E. Virginia Dobbin, G. P. Putnam's Sons, New York, 1958, 256 pages, $3.95.

Fat Consumption and Coronary Disease: the Evolutionary Answer to This Problem, by T. L. Cleave, Philosophical Library, New York, 1958, 40 pages, $2.50.

Hormone Production in Endocrine Tumours, edited by G. E. W. Wolstenholme and Maeve O'Connor, Ciba Foundation Colloquia on Endocrinology, Vol. XII, Little, Brown & Co., Boston, 1958, 351 pages, $9.00.

Maimonides, the Preservation of Youth. Essays on Health, Translated from the Original Arabic (Fi Tadbir as-Sihha) and with an Introduction by Hirsch L. Gordon, Philosophical Library, New York, 1958, 92 pages, $2.75.

Neurological Basis of Behaviour, edited by G. E. W. Wolstenholme and Cecelia M. O'Connor, Ciba Foundation Symposium, Little, Brown & Company., Boston, 1958, 400 pages, $9.00 (reviewed in this issue, page 69).

Old Age and Work, by Mogens Felbo, Ejnar Munksgard, Copenhagen, 1958, 236 pages, paper bound, d. kr. 30.00 (reviewed in this issue, page 68).

Portal Hypertension, by Alan Henderson Hunt, E. & S. Livingstone Ltd., Edinburgh and London, 1958, 230 pages, $8.50.

Readings in Medical Care, edited by the Committee on Medical Care Teaching of the Association of Teachers of Preventive Medicine, University of North Carolina Press, Chapel Hill, 1958, 708 page, $6.50 (Chapter VIII, Care of Long-Term Illness).

Rehabilitation of the Cardiovascular Patient, by Paul Dudley White, Howard A. Rusk, Philip R. Lee, and Bryan Williams, McGraw-Hill Book Company, Inc., New York, 1958, 176 pages, $7.00 (reviewed in this issue, page 68).

Strike Back at Stroke, U. S. Public Health Service Publication No. 596, 37-page pamphlet, available from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1958, 40 cents (reviewed in this issue, page 68).

The Care of the Geriatric Patient, edited by E. V. Cowdry, C. V. Mosby Co., St. Louis, 1958, 438 pages, $8.00.

The New Chemotherapy in Mental Illness, edited by H. L. Gordon, Philosophical Library, New York, 1958, 762 pages, $12.00.

Water and Electrolyte Metabolism in Relation to Age and Sex, edited by G. E. W. Wolstenholme and Cecelia M. O'Connor, Ciba Foundation Colloquia on Ageing, Vol. 4, Little, Brown & Company, Boston, 1958, 327 pages, $8.50.

What We Do Know About Heart Attacks, by John W. Gofman, G. P. Putnam's Sons, New York, 1958, 180 pages, $3.50.

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Section B

Psychological and Social Sciences, Social Welfare

Edited by

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VOLUME 14, SECTION B JANUARY, 1959 NUMBER 1

PSYCHOTHERAPY WITH GERIATRIC PATIENTS: A REVIEW OF THE LITERATURE

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This review is written with a view toward evaluating the current status of geriatric psychotherapy and outlining some of the major questions and problems that require research. The nature of geriatric problems will be discussed only insofar as such discussion is necessary in considering the rationale underlying particular therapeutic techniques; for more comprehensive reviews of geriatric pathology, the reader is referred to Shock's excellent bibliographies (61). Neither shall the scope of the geriatric mental health problem be discussed. The results of a recent study at a Minnesota state hospital (17) may be sufficient to indicate the magnitude of the problem. This study showed that while the percentage of people in the state over 65 years of age increased from 4.7 per cent to 9.0 per cent between 1920 and 1950, the percentage of patients admitted to the hospital for the first time who were over 65 increased from 12.4 per cent to 33.9 per cent during a comparable period. The emphasis in the present paper will be on therapeutic rationale and technique rather than on an evaluation of results, for well-controlled studies of the effectiveness of psychotherapy are few. Psychotherapy will be dealt with in a somewhat limited sense and excluded from consideration are such works as Lawton's effort toward defining a geriatric mental hygiene (42); the planning of social programs discussed by Donahue and Tibbitts (13, 14); the social group work programs for the normal aged, typified in the work of Kaplan (39) and Tarrel (68); the more medically oriented treatment programs of Clow and Allen (10, 11). While the above programs are psychotherapeutic in the broad sense, they may be differentiated from the face to face patient-therapist relationship which is here implied by the term psychotherapy.

A PIONEER SPIRIT

The first highly organized psychotherapeutic program for the aged was spearheaded by the energetic and apparently infectious enthusiasm of Dr. Lillien J. Martin, a psychologist who, after her own retirement, founded the San Francisco Old Age Counseling Center in 1929 and directed its activities until her death at the age of 92. The "Martin Method" of rehabilitation is described in three of her books (49, 50, 51). The approach was an essentially directive, inspirational one. It consisted of a series of planned interviews, five of which, according to Dr. Martin, were usually sufficient in 87 per cent of successful cases.

The first interview was aimed at personality evaluation and psychotherapy. It included the following procedures:

1. The client was asked to relate his life history in detail from his earliest memory up to the present. In so doing, the client was also asked to report any irrelevant side thoughts or images which might come to his mind in order to get at "subconscious complexes." The interpretation of dreams was not stressed because, ". . . in general, these are less enlightening to the counselor, since they tend to be recalled confusedly, unless they recur frequently and regularly" (49, p. 15).

2. A brief 20 minute series of tests was given, and the results were integrated with the life history and clinical observations to arrive at what Dr. Martin believed to be a comprehensive picture of the client's assets and liabilities.

3. The client was then prepared for psychotherapy by convincing him how ". . . imperative it is for him to banish all physical and mental resistance and adopt the 'will-to-do' attitude" (49, p. 28).

4. The counselor proceeded to analyze the results of his observations, the life history, and the tests with the patient in an effort to have him realistically appraise what had been maladjustive in his reaction patterns.

5. At the close of the first session, the client was provided with corrective slogans, e.g., "Each immoral act makes reformation more difficult," and "Sweep the cobwebs out of your mind." Psychological setting up exercises were also provided, e.g., "Have I today banished the purposeless activity called 'nervousness'?" and "Have I tried to solve rather than to forget my problems?" The client was finally sent home from the first interview with the strong assurance that ". . . he can and will make the effort for self-improvement necessary to gain for him a full and growing life functioning to replace the unsuccessful and unhappy existence that led him to seek counsel at the Old Age Center" (49, p. 30). Subsequent interviews were largely devoted to filling out charts by which the client could regulate his daily activities, budget, recreation, and future goals. Of her therapeutic approach, Dr. Martin said, ". . . troublesome states of mind and the complexes that underlie them are more quickly discovered by the Martin Method than by psychoanalysis. . . . When the core of these ideas is found the client must be helped to recognize its existence, to understand its implications in daily life, and to banish it from his mind" (49, p. 29).

In her own enthusiasm, Dr. Martin was perhaps overly optimistic. By current standards one interview that accomplished the taking of a life history, diagnostic testing, personality analysis, and the administration of corrective slogans must have been superficial. Nevertheless, by virtue of its vigor and optimism, the Martin Method may have had the therapeutic effects of overcoming pessimistic inertia and of convincing the client that he had his maladjustments corrected. Aside

from whatever results she might have achieved, Dr. Martin was a pioneer by virtue of her readiness to administer psychotherapy to the aged.

In spite of her efforts, Dr. Martin has had small influence on the development of geriatric psychotherapy, and she is very rarely quoted today. Perhaps a major reason for her lack of influence is that she seemed to proceed without an articulate theoretical framework, and hence there was little apart from her enthusiasm and devotion upon which others could build. Since her work was moved more by inspiration and faith than by psychiatric concepts or curiosity, no explicit systematic issues or research problems arose from her approach.

THE PSYCHOANALYTIC APPROACH

The early thinking about the extension of psychoanalysis to the treatment of the aged was marked with the skepticism of Freud, who listed at least three reasons why old people, as a rule, were not accessible to his therapeutic methods.

One reason involved the limitations of the aged ego or intellect. In this regard Freud ventured that, ". . . near or above the fifties the elasticity of the mental processes, on which the treatment depends, is as a rule lacking—old people are no longer educable. . . ." (18, p. 258). While, as will be seen in the discussion to follow, many writers continue to take note of such intellectual limitations, various modifications of psychoanalytic theory and practice have militated for diminished skepticism on this point.

Another caution raised by Freud was that ". . . the mass of material to be dealt with would prolong the duration of the treatment indefinitely" (18, p. 258). This objection appears to rest on an assumption that successful analysis requires a more or less complete anamnesis of the life history and a resolution of most, if not all, major conflicts experienced during a lifetime. In one sense, such an assumption appears unworkable, for it seems to depend upon a further assumption that there is little generality of personality pattern from life episode to life episode and that there is little generalization of therapeutic effect from one conflict resolution to another. Such a view would render all psychotherapies relatively ineffectual in the long run. In view of the over-all character of his theories, it is doubtful that Freud would today seriously subscribe to the assumptions of specificity which underlie the view that the elderly have too much life history behind them for successful analysis. In this regard, it is of interest that the argument of over-abundant life history has not been seriously considered by writers subsequent to Freud.

In an earlier paper, Freud had cited the "accumulation" argument discussed above, but had added: "With persons who are too far advanced in years it [psychoanalysis] fails because, owing to the accumulation of material, so much time would be required that the end of the cure would be reached at a period of life in which much importance is no longer attached to nervous health" (19, p. 245). The questioning of the importance of "nervous health" in the later years seems to constitute a third contraindication on Freud's part to initiating psychoanalysis with the aged, though the exact implication of the statement quoted is not apparent. Perhaps Freud meant that the mental health of the aged was not so highly valued as that of the young—a view which would imply a fundamental devaluation of old age. Without entering into the discussion of values which the issue implies, it might suffice to mention the title of Eissler's recent book, *The Psychiatrist and the Dying Patient* (15), as an indication that mental comfort, at least to some therapists, assumes great value as long as there is *any* mental life. On the other hand, this statement of Freud suggests an extremely cogent argument. In young persons, where there is anticipation of 30 or 40 years of happier living, the investment of time, money, and effort, and the partial delay of gratification may be as justifiable as the expenditure of resources for education. In older people the total economics of therapeutic investment is opened for review. Except for those exceptionally adventurous old people who can accept therapy as an exciting new experience, the trials of therapy are more heavily weighed. There may be an inclination on the part of both patient and therapist toward greater tolerance of pathology, which in turn is probably related to acceptance of the geriatric patient's dependency. Hollender has stressed this factor, venturing that, "Perhaps the best explanation for the fact that analysis is not a procedure for people in their fifties and over is that there is not enough to hope for in the future to provide the motivation needed to endure the tensions mobilized by analysis" (37, p. 342).

Also to be seriously considered in this regard is the emotional price paid when a patient reviews the failures of his past. It must be exceedingly difficult for a person nearing death to look back upon the bulk of his life as having been neurotic or maladjusted. It is this consideration that led Grotjahn (34) to suggest that it was important for the aged person to integrate his past life experiences as they have been lived, not as they might have been lived.

Abraham offered the first note of optimism regarding the analysis of the aged. He described the successful analysis of four neurotic patients about 50 years of age and concluded that ". . . the age of the neurosis is more important than the age of the patient" (1, p. 316).

Another of the early analysts to deal extensively with geriatric problems was Jelliffee, who echoed Abraham's thinking with the statement that "chronological, physiological, and psychological age do not go hand in hand" (38, p. 9). Armed with this dictum, Jelliffee proceeded with seemingly orthodox analyses of several older patients, and he published a description of several remarkably successful cases (38). But along with the successes, Jelliffee frankly related that in many cases ". . . the neurosis or psychosis was a better solution of their life difficulties than any that I, as an agent of reality, could offer" (38, p. 12). Fenichel (16) has more recently re-emphasized this caution as an important consideration in deciding upon the feasibility of psychoanalysis for aged patients. In contrast to more contemporary analysts like Alexander and French, to be discussed shortly, Jelliffee seemed most concerned with the suitability of the patient for the existing treatment, i.e., orthodox psychoanalysis, rather than considering modifications of his method. In this regard, he stressed the emotional fiber of the patient. "At one time I was even as brave as a lion in the belief that 'some acquaintance with the patient's unconscious would be of benefit to him in the treatment of his annoying symptoms.' Now I am much more inclined to tell my older patients that disease symptoms, physical often as well as psychical, are for the most part intuitively found

compensations for inner character defects; that if psychoanalytic principles be rigorously applied their most cherished beliefs and fundamental philosophies, and their consequent emotional valuations will be quite profoundly stirred and they will not like it; that they will probably curse me out and call me a quack or a shyster, but if they have real guts and can look themselves fairly and firmly in the face then much can be done for them" (38, p. 9).

In contrast to the criteria of analyzable patients suggested by the above writers, Kaufman (41) has more recently described a fairly successful outcome for two patients who, according to more traditional thinking, were relatively inaccessible on two counts; both patients were not only over 55 years of age, but were also in psychotic depressions when treatment was initiated. While Kaufman was quite cautious about making extensive generalizations on the basis of these two cases, he did venture that neither analysis was in any way complicated, and he felt that the relatively rapid change he observed in short periods did not sustain the contention that in older patients long periods of treatment are necessary before any changes take place. In a later paper dealing mainly with psychoanalytic theories of the aging process, Kaufman further questioned Freud's early views concerning the rigid ego of the aged. Kaufman observed that rather than being an immutable constant, "The rigidity seems to be a type of dissociation and the lack of elasticity really expresses a deeper repression of the anxieties with an increasing fixity of the reaction formations originally laid down as character traits" (40, p. 77). In a discussion appended to Kaufman's last-mentioned paper, Atkin expounded on this theme. Accepting Kaufman's suggestion that the rigidity is an ego defense, Atkin further ventured that it might be psychoanalytically treated as one might treat other defensive operations, rather than accepting it as an irreversible physiological impairment.

While earlier writers had called attention to the fact that their successes with geriatric patients were often in the nature of "transference cures," Grotjahn (33), in his discussion of the psychoanalytic investigation of a 71-year-old man with senile dementia, was the first to give strong emphasis to the real immediate needs the analyst was called upon to fill in the life of the geriatric patient. He wrote: "Not only is the senile person's relationship to reality changed by his psychotic withdrawal, but the reality situation itself is fundamentally changed by the biological and social dependence and helplessness of an old man. This fact and the genital impotence of old age make the analytic situation similar to the child analysis. In both, the analyst is not a more or less unreal image, but a vivid active part of reality engaged in the management of the patient's hospital life" (33, p. 80). With these remarks, Grotjahn seems to have anticipated the development of modified analytic techniques in the treatment of the aged.

MODIFIED PSYCHOANALYTIC TECHNIQUES

Alexander (3) dealt with the problem of the treatability of the aged within the scope of the general problem of treatability. In his discussion of modern, modified analytic techniques he delineated two broad types of treatment—insight therapy and supportive therapy. He spelled out the essence of insight therapy as the extension of ego control over previously repressed impulses which are released in the course of therapy. But where, for a variety of reasons, the ego is weak, then it is unreasonable to encourage release of impulses, since the ego will not be able to control them. In these cases the patient is given supportive therapy, where the patient's need for assistance is answered by actual guidance; where inferiority feelings are met with reassurance; where anxiety is relieved by the therapist's assuming a protective role; and where guilt is relieved by permissive attitudes. It is within the context of the above formulation that Alexander discussed the management of aged patients. While he did not state it explicitly, the implications of his approach clearly suggest that a primary consideration in treatment of the aged should be the degree of ego strength available. For example, he discussed the cases of two men, one 60 years and the other 66, who came to him shortly after their retirement from business careers (3). In the case of the younger man, the patient's handling of trial interpretations indicated a weakened ego-integrative capacity which, combined with other factors in the case, prompted a decision not to treat the patient. In contrast, the older client showed a more constructive handling of trial interpretations, and therapy was undertaken and successfully pursued.

In another work, Alexander and French (4) emphasized another important factor. They suggested that therapy usually implies some change in the life situation, and where no such change is possible, therapy may be contraindicated. While the authors were careful to point out that advanced age is not an absolute contraindication, they suggested that "prognosis is better for the young who have a far greater opportunity for change and who, therefore, usually respond more readily to treatment" (4, p. 97). (It is not clear from this formulation whether the possibility of change is important because external change helps the therapy along, or because therapy is to little avail without the possibility of external change.)

Fenichel (16) has been more explicit on this point. He suggested that in difficult living situations or where the patient was physically ill or crippled, the neurosis itself still may provide the best type of adjustment. Hollender has also elaborated on this theme with the following caution: "When a person has turned to the past or developed fixed ways of doing things to derive narcissistic gratifications or to protect against injuries to self-esteem, we should *not* tamper with these defenses unless we are sure that we can provide adequate substitutes for them" (37, p. 341).

With the path opened by Alexander and French for a frankly supportive type of analytic therapy, it remained for new workers in the area to give special attention to an elaboration of modified analytic techniques with the aged. Wayne (70, 71) has written on this topic and has offered the following suggestions: 1) Enough historical material is gained to permit a psychodynamic formulation and an understanding of transference behavior. "In the early interviews the patient's productions are guided by appropriate but unobtrusive questions in order to limit tangential material" (71, p. 102). 2) "Goal limitation is decided upon from the outset, as soon as an appraisal of the patient and his difficulties is made" (71, p. 102). 3) A crucial current problem may be used as the mainstream of therapy and can serve to keep the patient from feeling that therapy is becoming tangential by keeping in focus the problems he consciously recognizes. While material is not

deliberately avoided, no attempts are made to rekindle old conflicts, even though they may not have been handled in an entirely healthy manner. 4) The therapist's role is relatively active, not only in directing the course of therapy, but also in providing reassuring discussion, guidance, and even environmental manipulations where indicated. 5) The vis-a-vis position is used to decrease anxiety, promote a feeling of being understood, minimize overdependence, and lessen the quantity of repressive material. 6) "The patient must be given a readily perceivable part in solving his own problems" (71, p. 104). Some direct educational techniques may be used, such as realistic discussions of the cultural attitude toward the elderly and the physiology of the aging process. 8) Scheduling is flexible, and the general plan is to progressively decrease the number of weekly sessions. Therapy need not be finally terminated. "Tranquility—the goal of old age living, and the actual biologically quieter tempo of life can be accepted and expressed tacitly in the flexibility and wide spacing of interviews, as well as in the therapeutic atmosphere" (71, p. 104).

Meerloo (52, 53, 54) is another contemporary writer whose comments reflect the changed outlook of psychoanalysts toward the aged. Meerloo has displayed a persistent optimism on the subject and has offered several suggestions to the therapist treating the elderly. Like Wayne, he has emphasized the need for education, environmental modification (which he views as being largely the role of the home-visiting social worker), indeterminate termination, and a gentle handling of resistance. Like Grotjahn, he has called attention to the real, immediate way in which the therapist has to fill a need for interpersonal relationships which are otherwise missing in the patient's life. In contrast to Freud, who saw geriatric rigidity as precluding successful analysis of the elderly; and in contrast to Kaufman and Atkin, who saw the rigidity as a defense to be dealt with therapeutically, Meerloo spoke of a decreased resistiveness in the aged. He explained that there is less resistance, ". . . because approaching death presses them unconsciously to a reviewing of life and a comparison between early goals and actual achievements. My impression is that because of the weakening defenses, there is a better and more direct contact with the unconscious. Older patients react more easily to interpretations and feel more easily relieved by relating the actual conflicts with those of the past" (52, p. 335). Grotjahn has taken a similar view, observing that ". . . resistance against unpleasant insight is frequently lessened in old age. Demands of reality which in younger people are considered narcissistic threats may finally become acceptable. . . . It seems as if more or less suddenly resistance is weakened and insight occurs, just because it is 'high time' " (35, p. 420).

Meerloo has offered an explanation for a supportive approach with geriatric patients which is not inconsistent with his observation of decreased resistance in these same patients. He reasoned that the very weakness of the defenses which made it possible to reach the patient's unconscious also made it more difficult to diminish ties with the therapist. This is a challenging thought—that the older person is *too* open to self-examination. It seems to stand in fundamental disagreement with the experience of the majority of therapists who have spoken of the excessive needs of the aged patients to cling to a self-concept developed over a lifetime. The two points of view can, of course, be partly reconciled by viewing the rigidity as a defense against the excessive contact with the unconscious. Such a reconciliation, however, seems to obscure essential differences in the two points of view. For example, the overt behavior of geriatric patients is seen by one group of therapists as stubborn failure to consider oneself differently; and by the other group, as excessive self-examination. There is little doubt that some older patients are more open to self-inspection than some younger patients, and that some older patients are less open to self-inspection. However, it is not possible for older persons taken as a group to be at the same time both more and less open to self-inspection than younger persons, unless one is willing to hypothesize two distinctly different types of self-inspection. Therefore, the relative accessibility of insight to older people remains a major issue for geriatric psychotherapy.

Before leaving this point, it is of interest to note that in a more recent article Meerloo has observed that old people often show lessened suggestibility. He interpreted this positively, commenting that "Old age may represent a mental stability and continuity correcting the innate ambivalence and vacillation of man" (54, p. 73). To draw a composite, then, of the traits of elderly patients as Meerloo has described them, the picture is one of an individual who is ready to examine himself honestly and who has an inner stability that makes him resistant to suggestion. While these traits are by no means incompatible, the question arises whether Meerloo was more interested in picturing the most positive attributes of some geriatric patients or an overview of what is most characteristic.

With regard to transference dynamics in geriatric psychotherapy, Meerloo has, along with several other therapists, noted the frequent formulations of the reverse-transference, i.e., the patient views the therapist as his child. Meerloo (54) has described one case in which such a reverse-transference was not discouraged but utilized to further the therapy.

Although he stands as another of the contemporary analytic writers who propose the use of modified techniques and goals in the treatment of the aged, Hollender (37) seems to hold a much more reserved point of view than Meerloo. In fact, except for the advocacy of supportive techniques, Hollender seems to have taken a fairly traditional psychoanalytic view of the problem. For example, on the topic of rigidity, Hollender has written of the increased resistance to change and the increased difficulty in new learning with advancing age. Unlike Kaufman and Atkin, who have stressed its defensive aspect, Hollender has tended to view the rigidity as a more normal change—as both a physical and mental entrenchment which should be accepted by therapists as appropriate regearing, in much the same way as a move to a warmer climate might be considered beneficial. "Only when it [the entrenchment] is out of keeping with the real situation should it be regarded as an expression of an emotional difficulty" (37, p. 340). Except for the advocacy of supportive techniques, Hollender has remained in essential agreement with Freud. This is revealed in Hollender's concluding remarks on the topic, which express a view fairly representative of many contemporary practitioners toward geriatric psychotherapy: "In summary, it may be stated that while uncovering types of therapy can seldom, if ever, be used with older people, supportive forms of treatment selected

on the basis of a sound evaluation can accomplish much by helping to re-establish an emotional balance that has been shaken by the stresses of the latter years of life" (37, p. 342).

It is of interest to note that although Hollender and Meerloo appear to differ in their view of older patients and in their theoretical formulations, both advocate seemingly similar treatment techniques, i.e., support and a gentle handling of resistance. Hollender differs with Meerloo with regard to the interpretation of the reverse-transference. Hollender has ventured that, "The aged individual feels toward the therapist as he feels toward an adult son or daughter—but a son or daughter who would be like a parent to him" (37, p. 342).

Weinberg (72) is still another of the contemporary psychoanalysts who have proposed modified techniques in the treatment of the aged. He has advised that allowances be made for the possibility of unduly disturbing those patients who have severe psychosomatic conditions; and that allowances be made also for the reduced vigor, agility, and learning capacity of the aged. Like Wayne, he has also suggested that the therapist be relatively active and direct in the treatment of older people.

Lawton has proposed that psychotherapy with older persons "differs only in degree, not kind, from that employed with younger age groups. No new principles or techniques of therapy need to be involved, though old ones need to be modified" (43, p. 27). This generality has frequently been made about geriatric psychotherapy, but it appears to have little communicative value in itself, i.e., it depends largely on where one is willing to draw the line between what is a "modification" and what is "new." Lawton has also proposed that prognostic indicators for older persons are the same as for younger persons, but that fewer older persons "will qualify as suitable candidates for thorough-going psychological help as they get older" (43, p. 27). He has estimated that successful psychotherapy is possible with about 25 per cent of those older persons applying for therapeutic help, but he has not elaborated upon the kind of patients, type of therapy, criteria of success, or control observations which may or may not have entered into his estimation. While Lawton believes that psychoanalysis may be indicated for some older people, he stands with those who believe that more "superficial" approaches are generally indicated with the aged.

Lawton has contributed some clarification of the "rigidity" issue in geriatric psychotherapy by classifying the rigidity of older people into the following four types: 1) the diminished capacity for new learning which is based upon largely irreversible physiological changes; 2) the "rut formation" which develops through the continued practice of old habits; 3) the "protective" rigidity against change which is involved as a defense against fear; 4) the compulsive rigidity of perfectionistic persons. He has sketched out what must be accomplished to combat the various types of rigidity, although the explicit means of doing so was not always made apparent. In a discussion of attitudes toward geriatric psychotherapy, Lawton has pointed out that one of the reasons why older persons are reluctant to enter this kind of treatment is that they grew up at a time when psychotherapy was not widely accepted by laymen.

Lawton has also discussed the need for training in geriatric psychotherapy. While he has not gone so far as to propose specific training programs or procedures, he has noted some of the skills which need to be developed in geriatric psychotherapy; e.g., learning to differentiate between irreversible and reversible reactions, between true depressions and reactive depressions, and between repeated neurotic patterns and reactions to reality situations. Lawton's writings leave the impression that he fights as an ally at the side of the geriatric patient against the vicissitudes of reality, the unrelenting biological forces of decline, and the depreciating attitudes of society. In contrast to therapy with younger patients where one senses a pattern of continuing reaction and counter-reaction between patient and therapist, therapy with older patients often involves a sense of patient and therapist struggling together against forces hostile to both of them. Thus Lawton says, "Those who wish to aid older persons with their adjustments need the greatest amount of training and experience in learning how to help the older individual outwit and circumvent adverse community regulations and attitudes" (43, p. 34).

In contrast to those who have tended to minimize the importance of psychotherapy for the elderly, Lawton pointed out that the aged are often in highest positions of leadership, and as such, the consequences of their mental health are important for the rest of society.

Cutner (12) has provided an extremely interesting account of a 63-year-old neurotic woman who was treated by Jungian methods. Of special interest were Cutner's introductory remarks concerning the psychoanalysis of the aged. Following the teachings of Jungian psychology, she proposed that whereas the normal concerns of the first half of life are entrenchment in the outer world and the propagation and care of children, the task of the second half of life is individuation—the introversion of libido in the service of discovering and integrating the heretofore unconscious parts of the psyche. Of particular significance here is the contrast with the apparent goals of Freudian therapy. By comparison, the Freudians appear much more oriented toward youth, i.e., the emphasis is on contact with reality, affectual contact with other people, and productivity. Thus, for example, many Freudians see therapy with the aged pessimistically because of the decreased opportunity for libidinal gratification for these patients. For the Jungian psychologist, the task for the aged person has a merit of its own. Old age is the time of life for a person to come to know himself, rather than merely to attempt a reconciliation with an environment in which he has difficulty achieving the most desired forms of productivity and emotional fulfillment. While contact with the unconscious is a most important method for the Freudian, the method is directed largely toward the goals of youth. For the Jungian, contact with the unconscious becomes the goal itself.

Thus, while contemporary psychoanalysts have tended to think in terms of limited goals, Cutner's paper raises the question of *different* goals. This point has been most recently raised by Grotjahn who, although himself a Freudian, said, "The task of integrating one's life as it has been lived and the final acceptance of one's own death are problems of existence. To deal with them is the great task of old age. They are essentially different from the tasks of infancy, childhood, adolescence, and maturity" (35, p. 420).

To summarize thus far, the history of the psychoanalytic movement in regard to treating geriatric patients may be seen as having started with Freud's pessi-

mism, a pessimism which was shortly thereafter mitigated by the initial attempts and successes of analysts like Abraham and Jelliffee. Through these early years, the keynote of analytic treatment of the aged was that chronological age did not of necessity involve a deterioration of those intellectual and emotional capacities required for analysis, and hence *some* older persons could successfully undergo orthodox treatment. Later, the general evolution of modified analytic techniques under the guidance of Alexander and French prompted explorations of new approaches which would be applicable to a wide variety of geriatric problems. Therapists like Grotjahn, Wayne, Meerloo, Hollender, Weinberg, and Lawton used modified analytic approaches to the treatment of the aged, approaches which stress support and the active participation of the therapist. Still, as Hollender has suggested, there is no intrinsic contradiction between the early pessimism of Freud and the active efforts of contemporary psychoanalysts toward treating older patients. Freud was pessimistic in regard to treatment by orthodox methods toward a psychoanalytically ideal goal of bringing repressed material to conscious awareness and control, in order to attain greater libidinal satisfaction in reality. Whenever modified approaches have been attempted, they have generally been modified either in accord with more limited goals, or with the support of defenses, or they have relied upon direct intervention and environmental modification by the therapist. To the extent that these modifications are brought to bear, the pessimism of Freud concerning more ideal goals still obtains. A Jungian approach, on the other hand, has raised some new considerations regarding the goals of geriatric psychotherapy.

Several unresolved issues still pervade psychoanalytic thinking, then, many of which may be amenable to research. To restate some of them briefly, there are questions regarding intellectual efficiency, capacity for insight, motivation for and resistance to change, opportunity for libidinal gratification, and the choice of goals. Since these are questions which, in the main, confront the whole field of geriatric psychotherapy, these questions will be raised again in the last part of this paper.

GOLDFARB'S BRIEF THERAPY

While the approach of Goldfarb is based largely on psychoanalytic thinking, it is, more than any other approach, specifically oriented to the aged; and it has evolved in such organized form that it is deserving of separate attention. It is a therapy, furthermore, used with the brain-damaged aged who, in Goldfarb's view, present a most important and most difficult problem in the area of geriatric psychotherapy. Working in a home for the aged, Goldfarb and his associates have devoted themselves to the development of a practicable individual psychotherapy for their clients, so that, judging from the literature, they stand among the most experienced workers in the area. In comparison to the one or two therapy cases discussed by most of the previously-mentioned writers, Goldfarb and his associates speak from experience with over 100 cases, more than two dozen of which are individually reviewed among their several published articles (25, 26, 27, 28, 29, 30, 31, 32, 60, 69).

While it is true that the very nature of brief therapy allows for an easier accumulation of case material, the very accumulation reflects the fact that geriatric psychotherapy has reached a certain level of maturity—for not more than a decade ago therapy with a person over 65 was generally viewed as a somewhat novel experiment. Now, in the "Brief Therapy" of Goldfarb, there is at least one approach that is something more than an extension of an old technique to a new population. It stands as a landmark in geriatric psychotherapy, for it has developed from a formulation of the crucial problems of the aged, from a consideration of the resources older people are likely to bring to a therapeutic relationship, and from an appraisal of the practical problems involved in the geriatric treatment situation.

The major point of departure for Goldfarb is the dependency of the aged, dependency which in much the same way as earlier writers, he attributes to somatic changes, intellectual impairment, and socio-economic and personal losses. However, whereas previous writers have generally responded in one of three ways, i.e., either with discouragement as to what few resources remain for therapeutic work, by promoting acceptance of the dependency, or by providing real gratification for dependency needs, Goldfarb has deliberately attempted to use the increased dependency of the aged as a therapeutic resource.

Reasoning that the increased dependency makes the older person especially prone to view the therapist as a parent-figure, Goldfarb attempts to encourage this misperception to the extent that the patient develops the illusion that he is actually dealing with a very powerful parental authority who is capable of wielding great influence in his life. Once the illusion is firmly established, it is then used to provide gratification of emotional needs for punishment, affection, respect, and protection. Goldfarb claims substantial success with his techniques even though contacts are usually extremely brief, i.e., five- to fifteen-minute interviews once a week or less.

In his brief interviews, Goldfarb attempts to give the patient the feeling that a protective parent has been found. While little in the way of explicit, concrete aid is given in these sessions (Goldfarb at the same time emphasizes that in a wide variety of disorders, other types of therapy must accompany the psychotherapy) the therapist apparently behaves in such a manner as to leave the implication that such help can be forthcoming. With the patient who had never been able passively to enjoy a dependent position and who characteristically had to fight with others to gain gratification, Goldfarb attempts (partly by granting him small concessions) to create in him the feeling of having triumphed over the parent and therefore of having won control of the resources of gratification.

Several positive aspects of Goldfarb's approach immediately appear: 1) The therapy takes into account the increased dependency of the aged and hence, unlike some other approaches, it makes little demand for creative emotional resources within the patient. 2) The therapy is carried out almost entirely on the level of relationship, so that there is little demand for the intellectual resources which are required by insight and introspective therapies. Thus, the intellectual intactness of the patient becomes of relatively minor concern as compared to most other therapies. 3) The therapy is not structured in terms of self-reappraisal, so that many of the defensive resistances ordinarily stirred by psychiatric attention are circumvented. 4) The therapeutic regime is practical in terms of the amount of the ther-

apist's time involved with each patient. 5) According to Goldfarb, the brevity also makes the therapy more practical from the point of view of the patient with shortened life expectancy.

On the other hand, there are objections to Goldfarb's approach. In a discussion appended to a paper by Goldfarb and Sheps, Stieglitz has commented, "Notably lacking was any voluntary effort and any encouragement toward a *mastery of self*. The patient's self-esteem was bolstered by deliberately cultivating the illusion of victorious mastery over the parent-surrogate therapist and others. So far as I can detect, the therapist did not transmit any of his interest and desire to be helpful to the patients so that they might wish to help others in their intimate community and thereby enrich their sterile lives with purposefulness. True and constructive satisfactions can be developed, though perhaps not as quickly or easily as illusions can be fostered" (31, p. 218).

Certain of Stieglitz's objections seem of secondary importance. His objection to the lack of encouragement toward "mastery of self," might be countered with the argument that while therapists tend to agree that there is a quality, or faculty, of self-directedness in people, there is no widespread agreement as to how self-directedness is achieved. It does not seem unreasonable that even though Goldfarb's approach begins with the encouragement of an illusion, the resulting relief from tension and unhappiness might serve to liberate self-mastery in the patient. Certainly this argument seems as plausible as the suggestion that self-mastery can be attained by a therapist's "encouraging it." If anything, modern therapeutic practice has evolved as a reaction against the apparent unproductivity of the "pull yourself together" approach to emotional disorders.

Stieglitz objected that Goldfarb's approach does not make patients socially productive. Yet patients who have the illusion of being well protected, or the illusion of being in control of the sources of gratification, may feel well enough endowed themselves to be able to turn their attention to helping others. Goldfarb has reported instances where patients become more helpful in the institution following brief therapy.

There nevertheless remain certain potential weaknesses in Goldfarb's approach. While no data are available for comparing the results of brief therapy with those of other approaches, it would appear on rational grounds alone that:

1. Since the therapist becomes such a potent productive figure in the mind of the patient, it is possible that the patient may interpret the occurrence of difficulties in his everyday life as a sign of a waning of the therapist's interest or power. This could serve to magnify distress or to send the patient scurrying back repeatedly to the therapist for reassurance. Goldfarb, while pointing out that "success breeds success," and while reporting averages of only 5 to 9 treatment sessions for various groups of patients, does go on to report: "However, when the defects of resources are so great as in the brain-damaged aged person, it cannot be expected that realistic mastery can continuously take place and the cycle cannot be self-perpetuating. Then the psychotherapeutic effort must be a continuous or recurrent reinforcing technique" (32, p. 918). Thus it would appear that in Goldfarb's own experience, continuous reinforcement has been necessary only with the patients who have minimal resources.

2. The efficacy of brief therapy may be somewhat limited to institutional settings where the psychiatrist's position on the staff gives him real power with which to enhance and perpetuate the illusion to be fostered; where the therapist can be on hand whenever reinforcement of the illusion is necessary; where problems of referral, motivation for treatment, and accumulation of diagnostic information are minimal; and where reports from institutional personnel can substitute for the extended periods of appraisal of therapeutic progress which would be required in out-patient treatment.

3. The solution that is based upon illusion is nonreactive to the original source of difficulty, difficulty which may continue to stand as a potential threat to the patient or those around him. The facility with which it can be administered threatens to seduce therapists into using this approach, even where the potential for realistic solution by the patient, therapist, or societal forces is still substantial.

It is difficult to assess the present status of Goldfarb's approach among geriatric psychotherapies. There has been little discussion of it in the literature by those outside Goldfarb's immediate group. While many therapists may use similar methods, it is doubtful that many of them do so with Goldfarb's conceptual framework clearly in mind. In comparison with other approaches, it must be said that Goldfarb's concept of geriatric treatment is relatively straightforward. Two major issues need resolution. First is the question of the efficacy of the treatment; and while Goldfarb has presented figures describing the relative percentage of successful and unsuccessful cases, his methods of evaluation lack certain controls that would lead to undisputed acceptance of his conclusions. Second, there is the question of the long-term wisdom, irrespective of immediate gains, of using an approach based upon the creation of an illusion.

OTHER APPROACHES

There are several therapists whose work with aged patients does not seem to fit clearly into one or another "school" of therapy, or whose reports have been more in the nature of comments on geriatric psychotherapy rather than developments of systematic approaches.

Noting that old people are often confused, failing in memory, and suffering from sensory impairments, Stieglitz campaigned for clarity and simplicity in giving the patient instructions "on how to live" (64, p. 107). While Stieglitz appeared to take a paternal or "expert" role in instructing his patients, the stated rationale of his approach seems very different from that of Goldfarb. For example, Stieglitz emphasized, ". . . let us be honest. Mature individuals accept reality far better than the young. They are entitled to honesty, and they are entitled to be told that there are limitations on what can be accomplished. We should not promise more than what we have a right to expect" (64, p. 107). In general, Stieglitz's was a teacher-student relationship to patients, with the therapist providing the patient with clear, concise, "honest," information on how to live a healthy life. While his intent and stated methods appear to be very different from those of Goldfarb, similar factors may be involved in both approaches. For example, beyond the specific information given them, Stieglitz's patients must have derived considerable comfort from the feeling that an authoritative father-figure was interested in them.

Offenkrantz (5) has made some points similar to those of Goldfarb. He has suggested that the geriatric patient needs the same things from the therapist that a child needs from his parent, i.e., a dependent relationship and the feeling of being appreciated, cared for, and important. In similar fashion to Goldfarb, Offenkrantz has ventured that the therapist could allow those old people who have never learned consciously to enjoy dependent relationships to be quarrelsome, demanding, contentious, and unconsciously dependent.

The approach of Rockwell was based largely on the technique of distributive analysis and synthesis advocated by Adolph Meyer. Rockwell explained the approach as follows: "This consists of an analysis of all the factors involved, starting from the complaint, and taking into consideration the psychodynamic and somatic features, the situational conditions, and the constitutional make-up. Each interview is terminated with a constructive formulation synthesizing the material covered. The analysis is distributed along the lines suggested by a careful anamnesis and by the subjective needs of the patient as they become apparent during treatment. The physician assumes full obligation for the twenty-four-hour day of the patient and utilizes data collected currently by nurses or other observers" (57, p. 427). While Rockwell placed great emphasis on understanding the total life situation of the patient, he gave little explanation of how such understanding is to be utilized. Much use was made of manipulation of the situational setting, drugs, and diet, but Rockwell gave no description of a general rationale underlying the management of the psychotherapy itself.

If there is any general characteristic of Rockwell's approach which distinguishes it from others, it is that it seems to rest heavily on the repression of disturbing material. For example, in discussing the hostile patient, Rockwell proposed that ". . . it is helpful to discuss neutral topics and to avoid contradictions and arguments" (57, p. 430). In proposing occupational therapy for apathetic patients, Rockwell noted that one of the beneficial effects of reviving an old interest of the patient's was that it provided "a good neutral topic for discussion" (57, p. 435). With regard to sexuality, the comment was made, "The analysis of sexual dynamic factors in the more sweeping types of personality disorders, if indicated at all, is carried out cautiously during the period of convalescence" (57, p. 433). This last quote reflects another prominent, although implicit feature of Rockwell's approach, i.e., the tendency to avoid direct psychotherapeutic attack upon severe pathology. It is as though acute symptoms were viewed as storms to be weathered, rather than to be treated. Thus, "Any attempt to study the dynamic factors involved in the attitude of aversion should be delayed until the psychosis in which it occurs has disappeared" (57, p. 431).

Mittelman (55) has discussed psychotherapy with geriatric patients who suffer from psychosomatic disorders. He delineated two types of psychosomatic disorders: 1) Those which are not related to the aging process as such, and are therefore similar to psychosomatic disorders which might occur at any age; and 2) those which represent aggravations of and reactions to functional and structural disturbances connected with aging. With the first group, Mittelman suggested that psychoanalytic treatment could proceed in much the same fashion as with similar disorders in any age group. He held that prognosis was generally as favorable here as with younger patients, especially with those older patients who came for consultation and who agreed to treatment. Where the psychological disorder was related to organic malfunction associated with aging, e.g., coronary disease and hypertension, Mittelman advised that psychotherapy should proceed concomitantly with medical treatment, or, if the patient had had a severe organic attack, then psychotherapy should proceed as soon as convalescence sets in. In this latter group of patients, Mittelman has advised more caution in dealing with any topic likely to cause an emotional crisis lest the physical condition be aggravated. Within the limits of this caution, Mittelman expressed optimism with regard to reducing the functional features of the disorder. He was much more pessimistic when organic brain damage was involved. In this regard he ventured that the most that could be done was to decrease the patient's irritability and moodiness through use of the transference relationship, and that a major reliance would have to be placed upon environmental modification, drugs, and institutionalization.

Cameron (9) presented what are perhaps the most convincing arguments regarding the presence and etiology of rigidity and intellectual impairment of the aged. In contrast to writers who have spoken of instances of flexibility and unimpaired intelligence in individual geriatric patients, Cameron has cited evidence from experimental research to show that old people, as a group, show inflexibility and intellectual impairment. While granting that personal defensiveness and adjustive factors are involved in the old person's resistance to change, Cameron has emphasized that ". . . quite apart from personal and emotional involvement, there are certain inevitable deficiencies in performance with age which are dependent upon cellular and humoral changes. These have been shown to affect impersonal as well as personal activities, unemotional attitudes as well as emotional. Older persons often place greater reliance upon already fixed habitual attitudes and routines for the simple reason that they are incapable of learning, retaining, and utilizing new ones without considerable effort, and even then only to a limited degree" (9, p. 224).

Cameron has proceeded to spell out the implications of this view for therapy as follows: "If a large proportion of older persons are biologically incapable of adapting successfully to certain kinds of novelty, and this can be determined for the individual case, it is of little use to attack the problem as primarily one of anxiety and inadequate repression. More of the attention and effort of the patient, the relatives, the social worker, and the therapist can then be focused upon the development of greater tolerance toward such incapacity on all sides and particularly on the part of the patient himself, and upon exploring the possibilities of ameliorating its effects through introducing more flexibility into the environmental arrangements" (9, p. 213).

There are other authors whose contributions to the literature on geriatric psychotherapy, while more limited in scope, are of interest here. Gitelson (24) and Aldrich (2) have discussed the role of medical practitioners in the management of emotional problems of old people. Lokshin (48), Herkimer (36), and Ryder (59) have discussed social casework approaches to geriatric problems, pointing out advantages of counseling with several family members, especially the geriatric patient's

grown children. Some general comments on the increase of optimism in the psychotherapeutic treatment of the aged were made by Ross (58). Brenman and Knight (8) have given an especially interesting report of the successful treatment by hypnotherapy of a 71-year-old woman suffering from hysterical psychosis.

Stern (65, 66) discussed work with the aged in an old age counseling center. Ginzberg (20) stressed the use of environmental modification in psychological approaches to the aged. In this regard, he urged that, "If with younger individuals the main task is to help them adapt to environmental difficulties, it is the other way around with elderly patients—we must try to adapt the environment to them" (20, p. 42). One of the measures advocated by Ginzberg was that in cases where underlying factors were not clearly understood, the therapist should always side with the elderly person in any conflict with relatives or supervisors. Ginzberg has also written several articles (21, 22, 23) discussing the maintenance of therapeutic attitudes in psychiatric geriatric wards. Aronson (6) has discussed the same problem with reference to homes for the aged.

GROUP APPROACHES

Group therapy with the aged will be dealt with only very briefly. Smith, Bryant, and Twitchell-Allen (63) reported on a four week program of intensive resocializing activities for 43 elderly psychotic women, and Silver (62) reported on group psychotherapy with senile psychotic patients. Both studies claimed success in improving the behavior of patients.

Linden (44, 45, 46, 47) has provided the most extensive reports of group therapy procedures with the aged. Working with female patients in a state hospital, Linden provided data indicating that his procedures had been successful in improving behavior and in increasing rates of discharge from the hospital, although he was quick to point out the lack of control measures in his evaluations. There seems to be no single systematic approach in Linden's work. He himself has explained that, "Since it was found expedient to use almost every method of group approach at one time or another, the process came to be known as 'opportunistic group therapy'" (44, p. 163). Of note was the use of the group sessions to provide real, immediate social satisfaction. For example, "Contrasting with traditional individual and group psychotherapy, an aura of serious effort was not regarded as a *sine qua non*. Every opportunity for light-hearted fun and laughter was exploited to the fullest" (44, p. 163). Linden's experience showed that usual group therapy methods of allowing topics of discussion to come from the patients were relatively ineffective with his aged female patients. Among the methods he used to stimulate the group were giving more or less didactic talks, calling on individual group members and questioning them about biographical items, chiding patients with good-humored sarcasm, and using a female co-therapist. In one of his papers (47) Linden has presented an extensive discussion of the various transference reactions encountered in geriatric patients.

Rechtschaffen, Atkinson, and Freeman (56) have described an intensive treatment program for geriatric patients in a state hospital where group and supportive individual therapy were utilized along with an organized ward program which included occupational, recreational, and work therapy approaches. The rate at which these patients were discharged from the hospital was increased by over 300 per cent following the initiation of the program, although it is difficult to determine how much of the increase in discharge rate resulted from the therapy *per se* and how much from the intensive effort to place patients out of the hospital whenever this was considered advisable. The results of a follow-up study (7), which showed no improvement on a behavior rating scale after treatment, would tend to support the hypothesis that the latter factor was the more important.

It is of some interest that more attention has been given to the systematic evaluation of therapeutic outcome among the group approaches as compared to the individual approaches, probably because group approaches lend themselves more readily to the accumulation of large samples and the establishment of control groups or base rates. This is true at least in institutional settings.

COUNTERTRANSFERENCE PATTERNS

Various writers have discussed countertransference phenomena in geriatric psychotherapy, i.e., the emotional reactions of the therapist to the patient, and the topic appears important enough to warrant separate discussion.

Stern, Smith, and Frank (67) called special attention to the anxiety aroused in the therapist by the unconscious identification with the helplessness of some older clients. Along with Meerloo (53), they spoke of the wounds to a therapist's narcissism that are involved in dealing with irreversible situations, e.g., the approaching death of a client. Stern, Smith, and Frank have also referred to countertransference attitudes of hostility and guilt, but they were less explicit in outlining the dynamic structure of these reactions.

Meerloo (54) and Grotjahn (35) discussed the anxiety that is aroused in dealing with the sexual problems of the aged. Meerloo observed that the same kind of resistance that Freud met in calling attention to sexuality in children is now being met with regard to the aged. Meerloo has elaborated on the confusion and shame that sexuality produces in the aged and has lamented that, "Even today medical countertransference often denies sexual gratification to the old" (54, p. 78). Grotjahn has written, "A therapist who wishes to be older than he is may hide unresolved sexual conflicts behind such a wish. He hopes in an unrealistic way that the old persons will live beyond sin and sex, like little angels. Such a therapist may not be tolerant and realistic enough to understand his elderly patients in one of their most important sources of conflict, guilt, and depression" (35, p. 422).

Much of countertransference in geriatric psychotherapy has to be understood in terms of the "reversed transference" constellation, i.e., the tendency of the older patient to view the therapist as his son. Since many of the therapist's reactions will undoubtedly be in response to such a perception of himself by the patient, some additional remarks on the reversed transference itself may be in order at this point.

Grotjahn (35) has provided the most extensive discussion of the reversed transference. He sees it as the Oedipus complex, from the father's point of view; and he advises that it be allowed to develop, and that it be interpreted and integrated into the entire experience of the patient, in much the same way that Meerloo has

proposed. Grotjahn's remarks on this topic are of such theoretical significance as to warrant the following extensive quotations:

"The patient is allowed to see in the therapist the younger person. He may later accept in his therapist the representative of the younger generation and perhaps of the future. It was once the task of the son to work out his conscious and unconscious relations to his parents. It is now time for the father to go once more through his unconscious relation to another man in reversed order. In relation to the therapist, he has once more the chance and task to analyze in the transference relationship the Oedipus complex, but this time in reverse. The father should not submit to the son, nor should he kill him like the father of Oedipus tried to do. The father should realize that his life may be continued in his son" (35, p. 423).

Important in the context of the present discussion are the countertransference reactions to the reversed transference. Once again, to quote Grotjahn:

"The good son-therapist should not feel guilty for being younger. If necessary, he may develop an almost paternal attitude. He must be secure enough to withstand the onslaught of the older patient's hostility and [the patient's] attempt to make the younger man feel guilty and defensive for being younger" (35, p. 423).

Wayne (70) is another who has discussed the countertransference patterns of avoidance and irritation that may result when unresolved hostility toward parental figures is projected onto the elderly patient.

Grotjahn (35) has also written about countertransference attitudes which may be based upon earlier relationships with grandparents.

This discussion of countertransference leads to the question of the extent to which theorizing about geriatric psychotherapy may be influenced by such countertransference attitudes. For example, some of the resistance to working with the aged may stem from anxiety aroused in therapists by dependency needs of aged patients. Giving help to an aged patient may be avoided because it symbolizes the relinquishment of dependency claims by the therapist himself. If we are caring for the parent, who remains to care for us? It is also possible that the anxiety aroused by hostility toward parent figures may lead to a watering down of the therapeutic process and to an exaggerated emphasis on supportive and covering-over procedures. Defending against his own anxiety, a therapist may propose only the most benign interpretations, and may assume an attitude of reverence toward an older patient that is out of keeping with the patient's actual readiness to examine himself. The question might even be asked, does the emphasis on supportive measures for older patients in part represent a tendency to provide a less valued form of therapy for a less valued segment of the population?

SUMMARY AND DISCUSSION

From a historical perspective, psychotherapy with the aged had a slow, pessimistic beginning. Then, as interest in the area developed, there was a wave of optimism about how accessible older people are to psychotherapy and about how much can be accomplished. In retrospect, much of this optimism seems to have been exaggerated, perhaps largely as a reaction to the previous neglect of mental health in older people. At present a more considered attitude seems to prevail, with several investigators attempting to develop concepts of geriatric psychotherapy consistent with clinical and experimental observations of the resources and limitations of the aged. The actual practice of geriatric psychotherapy is not as extensive as psychotherapy with younger patients, but considering population trends, the prevalence of maladjustment in the aged, and current attempts to change cultural attitudes toward the elderly, it would not be surprising if, before long, psychotherapy might be as widely applied to old people as it is today to children.

As we have observed, there are divergent conceptions of geriatric psychotherapy; yet there appears to be a general trend developing in actual practice. Although there are exceptions, current thinking seems weighted toward the belief that most older persons, as compared with younger, profit most from supportive approaches in which the therapist plays a more active role. Therapeutic approaches might be arranged along a continuum of the degree of patient participation, as follows: 1) insight approaches, 2) supportive approaches, 3) direct gratification and environmental modification, 4) illusion-of-mastery therapy.

In general, the trend has been to use approaches toward the last-named end of the continuum with the following characteristics of the aged being offered as reasons: the increased dependency which arises from realistically difficult circumstances; the immodifiability of external circumstances to which a neurosis may be an optimal adjustive mechanism; irreversible impairments of intellectual and learning ability; resistance (or lack of resistance) to critical self-examination; the economics of therapeutic investment when life expectancy is shortened. There is considerable disagreement as to what weight the various factors actually carry.

It will be readily agreed that older people vary greatly with regard to the strength of their internal and external resources. Some are intellectually alert and emotionally adventurous; others are obviously impaired. Some older persons have a number of choices open to them; others, for varying economic, physical, and social factors, are relatively frozen in a given situation. In view of such wide individual differences, it would be well for therapists to remain open to a variety of possible approaches to older patients. As a concomitant, it would be well to emphasize the potential contribution of diagnostic appraisals, including psychometric and social service evaluations, in deciding which approach is most feasible for which patient.

In a sense, the emphasis on individual differences begs important issues regarding what is most general or most characteristic of older people and what is usually the most effective treatment for them. There is no reason to discuss geriatric pychotherapy as distinct from any other psychotherapy, unless there is some assumption that there are, or should be, some distinctive features about it. Still the central issues and problems regarding those distinctive features remain unresolved. These unresolved issues may be enumerated as follows:

1. As is true for psychotherapy as a whole, systematic, controlled studies of the effectivenes of various treatments of older people are still lacking. Ultimately, there must be empirical grounds for predicting which type of treatment will work best for which type of patient.

2. There is still debate as to the extent to which the impairments of intellect and learning ability in old people are determined by dynamic or by physiologic

factors. As Cameron (9) has noted, research evidence favors the latter.[1] Some question remains as to whether the kind of intelligence and learning thus far studied experimentally is sufficiently similar to that involved in achieving self-insights to permit generalizations from the research to the therapy situation, but it would appear probable that a certain amount of generalizing from the test to the therapy situation is warranted.

3. There is a very active disagreement regarding the extent to which old people are open to self-examination. This problem should be amenable to research. It might be found that there is more variability among older than among younger persons, with impending death causing the frankest soul-searching in some aged patients, but causing massive denial in others.

4. Finally, there is the question of the goals of geriatric psychotherapy. The attainment of certain goals may be limited in very real and immediate ways by cultural attitudes. We refer now to the limitation that negative attitudes toward the aged in our society place upon the amount and kinds of happiness that can be achieved by old people. If, at best, social reality is cruel, what can therapy hope to accomplish? There is genuine despair when the therapist himself cannot visualize a happier life for the geriatric patient who is physically ill, mentally clouded, socially ostracized, and approaching death. When the values of our culture are largely those of productivity and vigor, what satisfactions can psychotherapy produce for the old person? This is more than a rhetorical question, for it may be the principal obligation of geriatric psychotherapy to investigate the gratifications that can be evolved for older persons. We are reminded of Eissler's pioneering explorations into the possible sources of libidinal gratification for the dying patient (15), a problem even more difficult than the one posed here. Perhaps the greatest benefits to come from geriatric psychotherapy will be in its influence on the goals for the aged, rather than in the attempts to squeeze some happiness for old people out of the currently rejecting milieu.

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REORGANIZATION OF PERCEPTIONS WITH AGE*

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A series of studies has been undertaken to determine the relation between age and modifiability of activity. In one study an age deficit was found in alternating from one arithmetic operation to another (6). A second study of the series showed that elderly subjects did not inhibit motor speed as readily as younger subjects (7). The present study was concerned with the ability to reorganize prior perceptions. Two perception studies involving elderly subjects, reported by investigators (1, 12) from another laboratory, may be said to involve aspects of the present study, namely, the difference between age groups in altering perceptual organizations.

Leeper (13) investigated the influence of prior perceptual and verbal preparation on the organization and the alteration of perceptions. One figure that he used was Boring's "my wife" and "my mother-in-law" (3), a version of which is shown in Figure 1A. As perceptual preparation for viewing the ambiguous figure, Leeper presented subjects with either a perceptually unambiguous "wife" or an unambiguous "mother-in-law." Similar unambiguous figures are presented here in Figures 1B ("wife") and 1C ("mother-in-law"). Leeper found evidence that prior perceptual preparation influenced the organization of the subsequent perception and made for difficulty in changing from this organization to the alternative one.

Using Figure 1, the present study compares two age groups with respect to the type of percept that is organized and with respect to the ability to alter or reorganize this percept after preparation.

METHOD

The 74 male volunteer subjects were divided equally into two age groups. The age range of the older group was 65-81 years; the range of the younger group, 19-34 years. Both the mean and the median ages were approximately 71 years for the older group and 25 years for the younger group.

The range of formal education was 0-19 years for the older group and 7-20 years for the younger group. Both the mean and the median years of formal education were approximately 11 years for the older group and 14 years for the younger group. All subjects except three were community residents. The three were in a home for the aged.

The materials used in this study were three photographs of ink drawings, each measuring six and a quarter by eight and a half inches. The photographs, presented in Figure 1, were made from those used by Carlson (8) for a different purpose. The three figures in this study were faced to the right rather than to the left.

The ambiguous figure (Fig. 1A), which could be seen either as a younger woman ("wife") or as an older woman ("mother-in-law"), was shown to each subject, and he was asked what he saw. If either percept was reported within 90 seconds, the subject was informed that "another picture" could be seen and was asked what it was.

If the subject did not perceive the second "picture" in 90 seconds, then either the unambiguous "mother-in-law" (Fig. 1C) or the "wife" (Fig. 1B), whichever was appropriate, was shown for an additional 9 seconds. If the subject did not perceive the "picture" in this photograph, then the features were pointed out to him. The ambiguous figure (Fig. 1A) then was presented again for 90 seconds, and the subject was asked what he saw. This procedure is different from that of Leeper, who used lantern projections of the figures for exposures of 15 seconds in different orders (13).

RESULTS

Table 1 presents the results of this study for both elderly and younger groups. The older group was divided into two subgroups based on level of education: subjects with 12 or more years of formal education and subjects with less than 12 years. The differences between the groups in Table 1 were tested either by chi

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square or, when the expected cell frequencies were less than 5, by Fisher's more exact method (9, pp. 96-97).

The elderly were less able than the young to reorganize the initial percept after being shown either Figure 1B or 1C. Table 1 shows that, with this perceptual preparation, 24 of 29 younger subjects reported the alternate percept, while only 8 of 34 elderly subjects reported it. This age difference is significant beyond the .01 level of confidence. Greater ease of perceptual reorganization for the young also was suggested by a finding, not shown in Table 1, that, while it was necessary to point out the features of the alternate percept in Figure 1B or 1C to 33 of the 34 elderly subjects (97 per cent), only 21 of 29 younger subjects (72 per cent) needed this help.

When the younger group was compared with the older subgroup with 12 or more years of formal education, statistical significance was still obtained ($p = .01$). No significant difference was found, however, between the more highly educated elderly and the less educated elderly in reorganizing the percept ($p = .11$).

A second aspect of the data has to do with the reorganization or the alteration of the percept when only a verbal suggestion was made that another percept was possible, prior to showing Figure 1B or 1C. Few subjects in either age group reorganized the initial percept with only the verbal suggestion. As indicated in Table 1, only 7 of 36 younger subjects, and one of 35 older subjects reported the alternative percept in this situation. This age difference missed statistical significance ($p = .06$). In

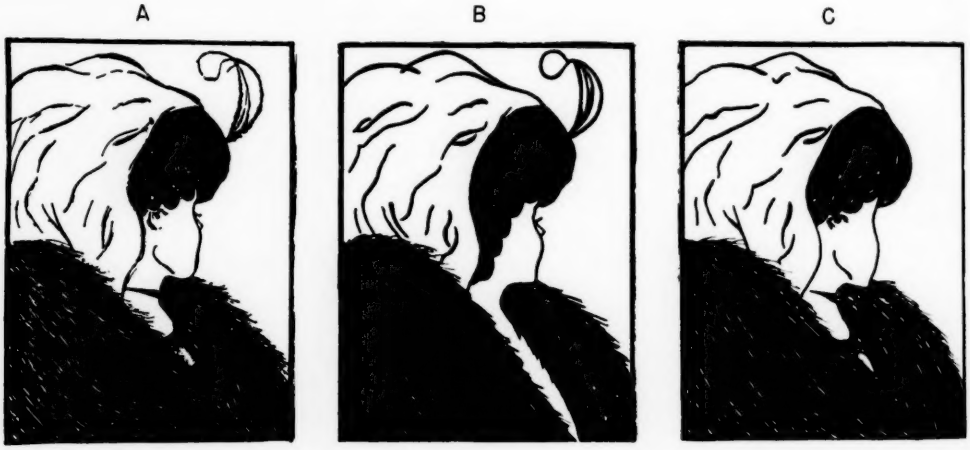

Fig. 1. Pictures used to measure ability to perceive and to alter original percept. (Permission to reprint the ambiguous figure [A] was given by the *American Journal of Psychology.*)

TABLE 1. DIFFERENCES EXHIBITED BY 37 YOUNG AND 37 ELDERLY MEN IN TYPE OF PERCEPT ORGANIZED AND IN ABILITY TO ALTER THE PERCEPT.

Age Group	Number Reporting as First Percept (Fig. 1A)			Reorganization of Percept with Only Verbal Suggestion		Reorganization of Percept after Seeing Fig. 1B or Fig. 1C	
	Wife	Mother-in-law	Neither	Number Reorganizing	Number Not Reorganizing	Number Reorganizing	Number Not Reorganizing
Young men[a]	28	8	1	7	29	24	5
Elderly men:							
Total group	33	2	2	1	34	8	26
17 men with high education (12–19 years)	15	1	1	1	15	6	9
20 men with low education (0–11 years)	18	1	1	0	19	2	17

[a] All but three of the young subjects had 12 or more years of schooling.

order to consider all the data related to the ability to alter or reorganize the initial percept, these subjects were added to those who needed to be shown either Figure 1B or 1C. It was found that 31 of 36 younger subjects were able to reorganize the percept, but only 9 of 35 elderly were able to do so. This age difference is significant well beyond the .01 level of confidence. An age deficit well beyond the .01 confidence level was also found when these younger subjects were compared with the 16 more highly educated elderly, 7 of whom were able to reorganize the percept in either situation. When the two education subgroups of elderly subjects were compared in this way, the difference was not significant ($p = .06$).

The third aspect of the data referred to the type of organization that was reported in Figure 1A. Table 1 indicates that 35 elderly and 36 younger subjects reported either the "wife" or the "mother-in-law." Although a higher percentage of elderly subjects initially reported the "wife," this age difference lacked statistical significance ($p = .09$).

DISCUSSION

The ambiguous figure is an imperfect one because the "wife" and the "mother-in-law" do not have equal probability of being reported. The younger group in this study reported the "wife" in 78 per cent of the cases when either percept was reported, while Leeper, with a different procedure, found this in 65 per cent of his subjects (13). The older group comprised 35 persons who reported either percept, and 94 per cent of these reported the "wife." In spite of the shortcomings of the ambiguous figure, the data of this study show clearly that the older group had greater difficulty than did the younger group in reorganizing or altering the initial percept.

This finding may be interpreted from different theoretical reference points. For example, the older group's greater difficulty in reorganizing or altering the initial percept may have resulted from a generalized deficit in modifying or inhibiting ongoing tendencies. As already indicated, evidence found in recent studies supports the hypothesis that older adults manifest such a deficit (6, 7). A related hypothesis is that older individuals may require more time to overcome the effects of an inaccurate expectancy (4). The implication is that set is more of a determinant in the behavior of the elderly than in the behavior of the young because more time may be required to reorganize the expectancy. Other recent evidence is a study by Heglin (11), which shows an age difference in problem-solving set.

Another interpretation of the results of this study involves the concept of perceptual difficulty. Ghent (10) compared groups of children of 4-13 years of age with respect to ability to perceive overlapping and embedded figures. She found an increase with age in the ability to unscramble the overlapping figures, and she hypothesized that this increase may have reflected an increase in perceptual span (number of lines that may be perceived and remembered simultaneously). Thus, to see both the "wife" and the "mother-in-law" superimposed in one figure may require a greater perceptual span than many of the older subjects were able to demonstrate. Evidence for a deficit in perception with age was found in two recent studies (2, 5). Relative inability of the older group to perceive both the "wife" and the "mother-in-law" in one figure was perhaps caused *both* by difficulty in perception and by difficulty in reorganization of the initial perception.

The last interpretation offered refers to a body of literature (e.g., 14, 15) that considers the effect of brain damage on the perceiving of overlapping and embedded figures. It is possible that the factors involved in the previous interpretations of the data not only are mutually inclusive but are also related to a change with age in the biological substrate. Experience, however, may also play a role, as is evidenced by the relative abilities of the education subgroups of elderly subjects to alter the initial percept. Whether the greater ability of the educated subgroup resulted from a selection factor is not known.

SUMMARY

Subjects in two age groups were presented with Boring's ambiguous figures of "my wife" and "my mother-in-law" and were compared with respect to the type of initial percept that was organized and with respect to the ability to report the alternative percept. The subjects were 74 male volunteers divided equally into two age groups, with medians of 71 and 25 years for the older and the younger groups, respectively. The data indicated that the older group was less able to reorganize the initial percept ($p < .01$).

Although both age groups tended to perceive the "wife" initially, the tendency was somewhat greater in the older group. The data also suggest that increased ability to reorganize percepts was related to increased education of the elderly subjects.

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BOOK REVIEWS

A Look at Thurston County's Older People. By CAROL LARSON STONE and WALTER L. SLOCUM. Bulletin 573, Washington Agricultural Experiment Stations, Institute of Agricultural Science, State College of Washington. May, 1957. Pp. 54.

This bulletin contains the principal findings of a study of living arrangements, use of time, and social participation among 549 residents aged 65 and above of Thurston County, Washington. The study claims to be, and is, little more than an assessment of some immediate practical needs reported by persons in a particular age group at a particular time and place. Indeed, while expressing the hope that the more general findings may have validity beyond county lines, the authors frankly caution that many of the specific findings are unique to Thurston County.

The first half of the pamphlet is devoted to a socio-economic description of the sample and a detailed accounting of actual conditions and felt needs among Thurston County aged with respect to physical health, income, housing, and transportation. A careful reading of this section, however, does reveal one or two findings of general significance. For example (although the authors do not so interpret their data), actual responses suggest that concern with physical health problems is considerably lower in this age group than has been generally supposed; and that the desire for productive employment is surprisingly low.

The findings on use of time and social participation, though unimaginatively reported and interpreted, are also of somewhat broader interest. Thus, with the single exception of gardening, the most popular leisure activities in this group are relatively non-interactive and consumption-oriented rather than interactive and production-oriented, e.g., reading, radio, TV, "going for rides." Few report hobbies or the urge to develop any. Of the minority (30 per cent) who express a desire for more recreational opportunities, most prefer types of activities that "are not [those] which a community would normally organize a program around." It appears that Thurston County's older people do not want to join clubs or go to work, but wish instead to travel, go fishing, watch movies, and go out dancing.

It seems clear that the authors expected loneliness to loom larger as a felt problem than in fact it does, and they tend to report their data as if these expectations had been fulfilled. For example, they report: "The fact that one out of ten cited loneliness as a problem suggests that not all had worked out satisfactory social adjustments." What about the nine out of ten who did *not* cite loneliness as a problem? The authors also make much of their finding that "almost two-fifths of the respondents said that religion was more important to them than it had been when they were younger." Why not emphasize that more than three-fifths said religion was *not* more important than it had been when they were younger? This is the well known "fully-only" technique of reporting statistics so that they seem to confirm preconceptions. Similarly, while conscientiously reporting declining church and organizational participation, the authors report no effort to discover whether or not this state of affairs affects the morale of aging people. They seem instead to assume that it does—adversely.

In summary, this pamphlet appears useful primarily as a handbook for public officials and private practitioners in Thurston County itself. As a scientific study of behavior and attitudes in this age group, it is unsophisticated and unimaginative. It ends with a series of "interpretations" that lack a theoretical framework and have the net effect of obscuring the significance of data, much of which is intrinsically quite provocative.

LOIS R. DEAN
Kansas City Study of Adult Life

The Family Life of Old People: An Inquiry in East London. By PETER TOWNSEND. Glencoe, Illinois: The Free Press, 1957. Pp. xvi + 284. $5.00.

Gerontologists have often discussed the importance of family and kinship ties in old age, yet the topics have been marked by a dearth of systematic social investigations. Thus Peter Townsend's monograph on the family life of older people in Bethnal Green, a working class section of East London, is a most welcome volume. The data for the monograph were gathered by intensive interviews with a random sample of older persons in the area. Approximately two-thirds of the sample were women, half of whom were widows. (Townsend's book is the second publication of the Institute of Community Studies; the first work, and a companion volume to the one under review, was *Family and Kinship in East London* by Michael Young and Peter Willmott.)

After a brief introductory section which discusses the study in outline, the locale and the demographic background, the work is divided into two major sections: I, "The Family Life of Old People"; and II, "The Family and the Social Problems of Old Age." In Part I, Townsend gives a detailed description of family life within the home in which the major theme is that the conjugal family may be independent yet maintain a high degree of interdependence with other kinsmen. He shows very clearly that many older persons do live near their relatives and many of these relatives, especially children, are seen regularly and frequently. Contrary to the picture drawn by many writers in gerontology, these older lower-class Britishers are not isolated from their children; the household of the older person is usually in close social contact with nearby households of kinsmen. Moreover, old people receive help from their relatives and often reciprocate with assistance to their children. This "two-way traffic," Townsend points out, is an essential feature of the family life of older people. The discussion points out how the extended family adjusts itself to the varying numbers, ages, and situations of its members. The one member who stands out predominantly in the extended kinship system is the old mother, "mum," who plays a crucial role in relationship to her children.

In Part II, Townsend turns his attention to the implications of retirement and poverty for the older person and his family. His findings clearly show that retirement has a much greater impact upon men than upon women, and he indicates how it may alter their lives and cut them off from associations formed at the place of work. Townsend's study reveals clearly the importance of the family as the one institution to which men and women belong from birth to death. Ties of friendship and neighborhood disappear, but the ties to family are more enduring.

Unlike many social scientists, Townsend is quite willing to offer proposals for social policy. His suggestions are tentative and not dogmatic; but he does make a number of concrete suggestions as to how the problems of isolation, loneliness, and economic deprivation might be handled in Great Britain.

The author offers a complete account of his methods in Appendices 1 to 4. Three full interviews with old people, examples of diaries which were kept by a small sub-group of participants in the study, and additional statistical tables add to the completeness of the report which, considering its brevity, is a model of thoroughness, accuracy, and clarity.

Since a comparative American study has not yet been conducted, a detailed analysis of the similarities and differences of American and British lower class families is not possible. Research studies in the United States indicate that while in some ways the American situation differs from the British, in other ways it is similar. Space precludes detailed comparison, but we might note, for example, that several American studies have found a strong desire on the part of older persons for a degree of independence and yet a maintenance of emotional support and affection. Some of the findings reported by Kutner and his associates, however, seem to vary from those of Townsend. In New York City ties of kinship do not appear to be as close-knit as those among the lower class in London. The findings from the Cornell studies of retirement indicate that retirement may not be as traumatic an experience as is indicated by Townsend for Britishers. These, and many other comparisons which might be made, suggest the desirability of a comparative study of lower class families in the United States and also studies of other classes in Great Britain and in the United States.

Townsend's work is a significant contribution to social gerontology and to the sociology of the family, and it deserves careful study by gerontologists and sociologists.

GORDON F. STREIB
Cornell University

Family Development. By EVELYN M. DUVALL. Chicago: J. B. Lippincott Co., 1957. Pp. vii + 533. $7.50.

Duvall has written a book which departs from the standard format of texts in the sociology of the family, and also from the traditional type of marriage textbook. She has used "the development task concept" to analyze the major stages of the family in terms of both individual development of family members and the family as a unit. The book consists of three parts. Part I, "Growing Families in Changing Times," discusses social change and family function, changing patterns in childbearing, social class differences in families, and family developmental tasks in general. Part II, "Expanding Families," covers the period when the typical family is established, through the period of childbearing and child-rearing, to the period when the children are teenagers. Part III, "Contracting Families," begins with a discussion of the period when adult children move out of the parental home to establish their own homes and families, followed by a discussion of families in the middle years and old age. This third section of the book is the one which may be of greatest interest to the readers of this journal.

Dr. Duvall has covered a great deal of professional literature as well as more popular kinds of material, and weaves all of it into a thoughtful and readable analysis following the developmental task scheme. There are times, however, when the critical reader may take issue with the way in which the author is able to list so fully and so assuredly developmental tasks for an aging husband and wife and for other family members.

Each chapter has a list of suggested activities which seem appropriate for student reports or projects. The references to the literature are complete, and each chapter has an extensive reading list. In most instances, it would have been helpful if these lists were annotated or classified in order to make them more useful for the reader. Like so many contemporary textbooks, the book has a number of photographs which, in view of the author's intended readership, seem somewhat out of place, since we are told that the book is designed for the professional worker.

GORDON F. STREIB
Cornell University

Retirement: A New Outlook for the Individual. By GIFFORD R. HART. New York: Harcourt, Brace & Co., 1957. Pp. viii + 179. $3.95.

This volume is written primarily for business executives and professional men in the middle economic brackets or better. While the author (a businessman who retired in his fifties) gives some consideration to the economic aspects of retirement living, he is primarily concerned with psychological preparation for retirement and with some of the experiences and adjustments which may be anticipated by men in retirement.

This is a well-written and concise treatment of these aspects of retirement as they relate to men who may well be more "work-oriented" than the average American.

ETHEL SHANAS
National Opinion Research Center
University of Chicago

BOOKS RECEIVED

BUREAU OF LABOR STATISTICS, U. S. DEPARTMENT OF LABOR. *Digest of One Hundred Selected Pension Plans under Collective Bargaining, Winter 1957-58.* Bulletin No. 1232. Washington: U. S. Government Printing Office, 1958. Pp. 71. 45 cents. (paper).

CONNECTICUT COMMISSION ON SERVICES FOR ELDERLY PERSONS. *Suggested Criteria of Design Standards for State-Aided Housing Projects for Elderly Persons.* Bulletin No. 1. Hartford, Conn.: The Commission, 1958. Pp. 8. (paper).

Creative Use of Sheltered Workshops in Rehabilitation: Report of an Institute Held for Regions I and II, Federal Office of Vocational Rehabilitation, Under the Auspices of Altro Health and Rehabilitation Services, Inc., New York, N. Y., September 9 to 13, 1957. New York: Altro Work Shops, Inc., 71 West 47th Street, 1958. Pp. 47. 50 cents. (paper).

CROOK, G. HAMILTON, and HEINSTEIN, MARTHA. *The Older Worker in Industry.* Berkeley: Institute of Industrial Relations, University of California, 1958. Pp. vi + 143. $2.00. (paper).

HEDGES, SID G. *Fun for the Not-So-Young.* New York: Philosophical Library, 1958. Pp. 142. $3.75.

MAIMONIDES, MOSES. *The Preservation of Youth: Essays on Health.* Trans. by Hirsch L. Gordon. New York: Philosophical Library, 1958. Pp. 92. $2.75.

Modern Maturity. Vol. 1, No. 1, October-November, 1958. Published every other month by the American Association of Retired Persons, Colonial Building, 15th Street, N. W., Washington 5, D. C., as a service to its membership.

Salute to the Aging: A Guide to New York State Services for Senior Citizens. Albany: Office of the Special Assistant, Problems of the Aging, State Capitol, 1958. Pp. 75. (paper).

SCUDDER, DELTON L. (Ed.). *Organized Religion and the Older Person: A Report on the Eighth Annual Southern Conference on Gerontology Held at the University of Florida April 10-11, 1958.* Vol. 8, Institute of Gerontology Series. Gainesville: University of Florida Press, 1958. Pp. x + 113. $2.50. (paper).

Selected Studies of Migration Since World War II: Proceedings of the Thirty-Fourth Annual Conference of the Milbank Memorial Fund, Held October 30-31, 1957, at the New York Academy of Medicine, Part III. New York: Milbank Memorial Fund, 1958. Pp. 244. $1.00. (paper).

SHELDON, HENRY D. *The Older Population of the United States.* New York: John Wiley & Sons, 1958. Pp. xiii + 224. $6.00.

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VOLUME 14, NUMBER 1
JANUARY, 1959

Section C

Organization Section
Index to Current Periodical Literature

VOLUME 14, SECTION C JANUARY, 1959 NUMBER 1

ORGANIZATION SECTION

GERONTOLOGICAL SOCIETY, INC. COUNCIL FOR 1959

President	Louis Kuplan (Sacramento)	Past President	Albert I. Lansing (Pittsburgh)
President-elect	Nathan W. Shock (Baltimore)	Treasurer	John E. Kirk (St. Louis)
	Secretary	Robert W. Kleemeier (St. Louis)	

	to serve through
Biological Sciences	
Warren Andrew (Indianapolis)	1959
Norman M. Sulkin (Winston-Salem)	1960
Clinical Medicine	
Robert T. Monroe (Boston)	1959
Leo Gitman (Brooklyn)	1960
Psychological and Social Sciences	
Gordon Streib (Ithaca)	1959
Ethel Shanas (Chicago)	1960
Social Welfare	
Ben L. Grossman (Chicago)	1959
Jerome Kaplan (Mansfield, Ohio)	1960
General Membership Division	
Helen Zollinger (Portland, Ore.)	1960
Herbert Shore (Dallas)	1961
Affiliate Organizations Division	
Harold E. Jones (Berkeley)	1960
Chairman, Research and Fellowships Committee	
Robert J. Havighurst (Chicago)	1961

PAST PRESIDENTS OF THE SOCIETY

William deB. MacNider	1945
Roy G. Hoskins	1946
Lawrence K. Frank	1947
Joseph C. Aub	1948
Clive M. McCay	1949
C. J. Van Slyke	1950
Robert A. Moore	1951
Ernest W. Burgess	1952
E. Vincent Cowdry	1953
Anton J. Carlson	1954
Ollie Randall	1955
William B. Kountz	1956
Robert J. Havighurst	1957
Albert I. Lansing	1958

Representative on the Governing Body of the International Association of Gerontology
Robert J. Havighurst 1958-1960

Representative to the American Association for the Advancement of Science
Nathan W. Shock 1959-1961

SUMMARY OF THE MINUTES OF THE THIRTEENTH ANNUAL MEETING OF THE COUNCIL AND MEMBERS OF THE CORPORATION OF GERONTOLOGICAL SOCIETY, INC.*

The meeting was called to order by President A. I. Lansing at 9:05 a. m., November 5, 1958, in Room 108, Hotel Bellevue-Stratford, Philadelphia, Pennsylvania. Members of the Council present were: A. I. Lansing, L. Kuplan, R. J. Havighurst, N. W. Shock, J. E. Kirk, W. Andrew, N. M. Sulkin, L. Gitman, R. W. Kleemeier, Ethel Shanas, B. L. Grossman, and W. M. Beattie, Jr. Members absent were: R. T. Monroe, J. Kaplan, H. Zollinger, H. E. Jones, and J. E. Anderson.

The Minutes of the Twelfth Annual Meeting of the Council and Members of the Corporation of Gerontological Society, Inc. were approved as published in the January, 1958, issue of the Journal of Gerontology.

Dr. Lansing reported that the Sub-Committee on Biological Sciences and Clinical Medicine of the Research Grants and Fellowships Committee has almost completed a survey of the status and prospects for research on gerontology in the United States. The work of this Sub-Committee was financed by a grant from the National Institutes of Health.

As Chairman of the Finance Committee, Dr. Lansing stated that he had been in close touch with the Ford Foundation but that they are not interested in giving support to the Journal of Gerontology or the Society, but rather that their interest lies in the social aspects of gerontology. Because of the death of Mr. Glendorn, the Society can expect no further funds from the Glendorn Foundation. A generous grant from the Forest Park Foundation, toward the support of the Journal of

* A full report is available upon application to the Administrative Secretary, Mrs. Marjorie Adler, 660 South Kingshighway Blvd., St. Louis 10, Mo.

Gerontology and the Newsletter, was gratefully acknowledged. The National Institutes of Health have continued to approve grants to permit the Society to invite foreign gerontologists to participate in the programs of the annual meetings of the Society.

Dr. Lansing suggested, and the Council agreed, if the Society were permitted to retain the unused balances from the two Glendorn Foundation grants, that this sum be placed in a Special Publications Fund. Overhead from existing and possible future grants will also be placed in this fund, the combined funds to be used for the publication of monographs, profit from the sale of which would eventually enable the publication program of the Society to become self-sustaining. Dr. Lansing mentioned that royalties from the publication of a book on one of the Glendorn grants were to be allocated to the Society and should also be placed in this Special Publications Fund.

Dr. Kirk, as Treasurer, reported that the finances of the Society are fairly satisfactory because of the Forest Park Foundation grant of $4,000 for the year and the increase in the number of memberships. The relatively small number of non-renewals gave a total increase of about 200 members receiving the Journal. As Editor of the Journal of Gerontology, he expressed his gratitude to Dr. Neugarten and Dr. Havighurst for their work on Section B of the Journal. So far, there has been little increase in the amount of advertising in the Journal.

Mr. Kuplan recommended that the Section on Social Welfare have a representative on Section B of the Journal. The Council referred the recommendation to the Editorial Board of the Journal.

It was recommended that the bylaws be altered to conform with the Statement on Procedure for Membership adopted last year and to notify all members to this effect prior to the next annual meeting in order that the change can be voted upon at the Business Meeting in 1959. Article III 2c of the bylaws would be changed from "Any person may be elected to membership by the vote or assent in writing of a majority of the Council. To be eligible for membership, an applicant must: (a) be interested in and sympathetic with the purposes of the Society as expressed in its Charter, and (b) be nominated by 2 Members of the Society. Dues of Members shall be fixed in accordance with Article XI of these bylaws" to "Action on applications for membership shall be taken by the Secretary on the basis of criteria which he and the Membership Committee believe are adequate. The criteria may differ for membership in the Professional Sections and in the General Member Division. All applicants of good character and definite interest in the field of gerontology shall be admitted to the General Member Division. Dues of Members shall be fixed in accordance with Article XI of these bylaws."

As Secretary, Dr. Shock reported that there were 258 new members receiving the Journal and 204 new General Members not receiving the Journal, with a combined total of paid memberships of 1697 plus a total of 147 in arrears in dues for one year. Membership in the Sections, as of November 1, 1958, is as follows: Biological Sciences, 186 Fellows and 34 Members; Clinical Medicine, 344 Fellows and 116 Members; Psychological and Social Sciences, 139 Fellows and 58 Members; Social Welfare, 147 Fellows and 53 Members, and General Section, 155 Members with Journal, 450 with Newsletter.

It was moved and passed that a membership list be published every two years in the Journal of Gerontology, giving the addresses of the members and the Sections to which they belong.

It was decided that records of the Society should be kept in the possession of the professional Secretary. At the discretion of the Secretary, all records older than 4 years can be destroyed, with the exception of financial statements and Minutes of meetings.

The report of the Editor of the Newsletter was accepted with commendation, and it was agreed that a letter expressing the Society's appreciation be sent to Dr. Kaplan. The suggestion was accepted that the pages in the Newsletter be numbered consecutively within each volume, beginning with the 1959 volume.

Mr. Kuplan presented a report on the 1960* meeting in San Francisco, August 7-12 inclusive, in association with the Fifth Congress of the International Association of Gerontology. Pittsburgh was affirmed as the 1961 meeting place. It is expected that the local group will finance the meeting costs as much as possible, but the Society will help to some extent as it has in the past.

It was moved and passed that the chairmen of certain committees serve a term of 3 years, as the Council finds necessary, for continuity of business of the Society. This currently applies to the Exhibits Committee, Finance Committee, Research Grants and Fellowships Committee, and three new committees: one for recommending the place of the annual meetings for Council action; a committee on the History of Gerontology, and a Committee on Public Relations. Provision for rotation among the membership of committees should be made by the Chairman so that the terms of all members of a given committee do not expire at the same time, and it was agreed that the chairman of the Local Arrangements Committee should be selected as soon as the place of an annual meeting was decided upon. Mr. Kuplan suggested the inclusion of a Sub-Committee on Social Welfare on the Research Grants and Fellowships Committee.

The Nominations Committee† recommended Dr. Shock for President-elect; Dr. Kleemeier for Secretary; Dr. Gordon Streib to serve the unexpired term of Dr. Kleemeier on the Council, and Mr. Herbert Shore as Council representative for the General Member Division. The report was accepted unanimously by the Council. Dr. Havighurst was appointed the Society's representative on the Governing Body of the International Association of Gerontology to serve through the Congress in 1960, and Dr. Shock was appointed the Society's representative to the American Association for the Advancement of Science to serve through 1961. Dr. Leo Gitman was appointed Chairman of the Exhibits Committee to serve through 1961.

It was voted that each Section of the Society be allotted $75.00 per Section per annum to be spent at the discretion of the Section, but that such funds would not be accumulative. It was pointed out that the Sections might have officers other than the two representatives on the Council, but that additional officers are not obligatory.

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* The 1959 meeting will be held in Detroit, November 11-13, at the Statler Hotel.

† Dr. Shock and Dr. Kleemeier were absent during the Council discussion of this report.

The budget, showing an anticipated deficit of approximately $4.000, was accepted, and it was voted that dues would remain the same as in 1958; i.e., $12.50 for Fellows and Members receiving the Journal of Gerontology; $2.50 for Members receiving only the Newsletter, and $10.50 for foreign Fellows and Members receiving the Journal. Members of affiliate organizations receive the Newsletter on payment of $1.50 per member by the affiliate organization. Suspension of dues for members temporarily out of the country was deemed to be an administrative matter.

A contribution of $50.00 to the National Society for Medical Research for 1959 and payment of dues (1 shilling, or 14.6 cents) to the International Association of Gerontology for each voting member of the national Society were authorized.

The charters for the Western Gerontological Society and the Florida Council on Aging as Affiliate Groups and the Texas Society on Aging as a Local Chapter were renewed for 1959.

Dr. Gitman's written report of the Exhibits Committee (including his recommendation that background draperies used in exhibit spaces be paid for by the Society), Dr. Kleemeier's report of the Newsletter Committee, and Dr. Anderson's report for the Sub-Committee on Psychological and Social Sciences of the Research Grants and Fellowships Committee were accepted. Dr. Havighurst was appointed chairman of the Research Grants and Fellowships Committee (1959-1951).

Dr. Anderson's resignation as Chairman of the Sub-Committee on Psychological and Social Sciences of the Research Grants and Fellowships Committee was accepted, and Dr. Kleemeier was appointed to fill this post. The Council authorized Dr. Kleemeier to request funds from granting agencies in the name of the Society to finance a series of research conferences on the place of substitute activities for work after retirement.

Under Additional Business and New Business, it was agreed to pay a part time assistant $1.75 per hour for a maximum of 1105 hours per annum. It was decided that institutional memberships would be accepted with the name of an individual, that only the President has the right to poll the Council (with the exception that the Secretary's and Administrative Secretary's version of the Minutes can be sent directly to the Council), and that when the Council is polled, the voting will be considered closed within 3 weeks of date of mailing. It was agreed that the requirement that officers of Affiliate Groups and Local Chapters be members of the national Society meant any voting member, not only Fellows of the Society, and that these groups should be polled for nominations when a vacancy occurs on the Council for a representative for these groups. Dr. Kirk was designated to explore the possibility of a Sub-Section on Dental Medicine, and the Council decided that consideration would be given to creating such a Sub-Section when a nucleus of 25 dentists, Members of the Society, expressed a desire for a separate Sub-Section. Consideration was also given to the possibility of changing the name of the Section on Clinical Medicine to Health Services and to include dentists, veterinarians, and nurses. This question was referred to the Section on Clinical Medicine for recommendations. It was agreed that designs for a corporate seal for the Society, bearing the numerals "1945" as prescribed by the Society's Certificate of Incorporation, be solicited. The meeting adjourned at 5:00 p. m.

Continuation of Council Meeting—The meeting was called to order at 4:40 p. m., November 7, 1958, in Room 108, Bellevue-Stratford Hotel, Philadelphia, Pennsylvania. R. T. Monroe and J. Kaplan were present, in addition to those members listed above, with the exception of B. L. Grossman, who was not able to attend the second meeting.

Dr. H. Sobel, representing the Western Gerontological Society, was also present at the beginning of the meeting and presented 4 recommendations: (1) that there be a mechanism for informing regional groups of the activities of the national organization, (2) that the Newsletter be used to give information regarding the activities of the regional groups, (3) that a portion of the dues paid by the regional groups to the national Society be rebated to support the activities of the regional groups, and (4) that the national Society serve as a stimulus to the regional groups. The Council agreed that (1) the Newsletter should continue to publish an abstract of the Minutes of the national meetings, (2) the Newsletter should reflect regional activities, but that it was the responsibility of the regional groups to supply the Editor with information, (3) a rebate would, in effect, constitute a reduction in dues, which had been set at $1.50 per non-member of the national organization to cover the cost of sending the Newsletter to these people and would not be possible, and (4) while the national Society does not have the funds to pay the traveling expenses to send national officers to the regional groups, the national Society will cooperate as much as possible in every way.

Reports from the 4 Sections were presented by their representatives on the Council:

Biological Sciences—Dr. Andrew reported that 10 applications for Fellowship had been approved. It was agreed that the Secretary of the Section, Dr. James Rogers (Louisville), should receive, from the Administrative Secretary, a list of the Fellows and Members in this Section in order to conduct a mail vote for nomination of a Council representative for 1960.

Clinical Medicine—Dr. Gitman reported that 11 applicants for Fellowship status had been accepted, and that Dr. Raymond Harris (Albany) had been nominated as the Section's representative to the Council for 1960-1962. Expansion of the Section, under a new name of Section on Health Service to include dentists, veterinarians, and nurses, was discussed. The Section did not think it desirable to alter its name or structure at the present time. It was recommended that the Program Committee give serious consideration to developing specific programs in dentistry, nursing, and veterinary medicine at the next annual meeting of the Society. If sufficient interest is evidenced, consideration could then be given to setting up separate sections or subsections for these groups.

Psychological and Social Sciences—Dr. Shanas stated that the Section had nominated Dr. Irving Webber (Gainesville), Dr. Marion Bunch (St. Louis), and Dr. Gordon Aldridge (East Lansing) for the Section's representative on the Council for 1960-1962. Mr. C. Tibbitts (Washington, D. C.), Dr. W. H. Reals (St. Louis), and Dr. Webber were suggested to represent the Section on the Historical Committee. Eight Fellowship applications were approved, one deferred.

Social Welfare—Mr. Kaplan reported that the Section

had elected a Chairman, Vice-Chairman, and Secretary, but had not had sufficient time to nominate a representative to the Council for 1960-1962 which would be taken care of by a mail ballot. The Section had voted to defer all 5 applicants for Fellowship status, and had discussed raising the level for Fellowship status in this Section. The Council accepted the Section's recommendation that the deferred applicants be so notified, this matter to apply to all Sections.

The Council voted in favor of Dr. Havighurst replacing Dr. Anderson, who had resigned as Chairman of the Research Grants and Fellowships Committee, for a 3-year period. Dr. Havighurst will serve as this Committee's representative to the Council from 1959-1961. Dr. Lansing was appointed chairman of the Sub-Committee on Biology and Medicine (1959-1961) and Dr. Kleemeier chairman of the Sub-Committee on Psychological and Social Sciences (1959-1961).

It was agreed that the Secretary and the Administrative Secretary should devise a brochure about the Society to be sent out with membership application forms, the brochure to be retained by the prospective member and the membership form completed and returned to the Society.

The Council authorized the appointment of a Committee on Public Relations. The chairman will serve a term of 3 years. The request of Audio-Briefs for suggestions from the Society of subjects and material on gerontology and geriatrics for 15-minute tape recordings was referred to the Committee on Public Relations by the Council.

A vote of commendation was accorded to the Program Chairmen, and instructions were issued for letters of appreciation to be sent to Dr. Andrew and Dr. Freeman.

The meeting adjourned at 5:45 p. m.

N. W. SHOCK, Secretary

SUMMARY OF THE MINUTES OF THE ELEVENTH ANNUAL BUSINESS MEETING OF GERONTOLOGICAL SOCIETY, INC.*

The meeting was called to order by President A. I. Lansing at 11:40 a. m., November 8, 1958, in the Ball Room of the Bellevue-Stratford Hotel, Philadelphia, Pennsylvania. Approximately 60 members were present.

The Minutes of the Tenth Annual Business Meeting were approved and the actions and recommendations of the Council (see above Minutes) were reported by the President, Secretary, and Treasurer of the Society. The report of the Corporation for 1957 was made available for inspection by members of the Society.

Dr. Havighurst, Chairman of the Nominating Committee, presented the slate recommended by the Council: President-elect, Dr. Nathan W. Shock; Secretary, Dr. Robert J. Kleemeier; Council representative for the Section on Psychological and Social Sciences to complete the unexpired term of Dr. Kleemeier (1959), Dr. Gordon Streib, and Council representative for the General Membership Division, Mr. Herbert Shore. There were no nominations from the floor and the slate was elected by unanimous vote.

After discussion from the floor, all actions and recommendations of the Council (see Minutes of the Council Meeting for details) were approved.

Dr. Herman Seidel (Baltimore) commented favorably on the Supplements to the Journal of Gerontology and urged their continuation. He also expressed the hope that full reports of the papers read at the annual scientific meetings of the Society could be published in a single volume. Dr. Lansing, as chairman of the Editorial Board, agreed to present the proposal to the Editorial Board for their consideration.

Dr. J. T. Freeman commented on the desirability of increasing the coverage of clinical problems in the Journal.

The following appointments were announced:

Chairman of Research Grants and Fellowships Committee, Dr. R. J. Havighurst, 1959-1961

Chairman of Sub-Committee on Biology and Medicine, Dr. A. I. Lansing, 1959-1961

Chairman of Sub-Committee on Psychological and Social Sciences, Dr. R. W. Kleemeier, 1959-1961

Chairman of Committee on Exhibits, Dr. Leo Gitman, 1959-1961

Society representative on the Governing Body of the International Association of Gerontology, Dr. R. J. Havighurst (through 1960)

Society representative to the American Association for the Advancement of Science, N. W. Shock, 1959-1961

The Council authorized the appointment of the following new committees; with the chairmen to serve a 3-year term 1959-1961):

Committee on Place of Annual Meetings

Committee on Public Relations

Committee on the History of Gerontology

The next annual meeting will be held in the Hotel Statler, Detroit, Michigan, November 11-13, 1959. In 1960, the annual meeting will be held in conjunction with the Fifth International Gerontological Congress in San Francisco, August 7-12, 1960. The 1961 meeting of the Society will be held in Pittsburgh. The specific dates will be selected by the Local Committee.

Dr. Herman Seidel commented on the rising interest of the American Medical Association in gerontology and suggested that the Gerontological Society should take steps to collaborate with the AMA Committee on Aging. Dr. Lansing expressed the opinion that the new committee on Public Relations would give careful consideration to this proposal.

Dr. Anthony Salamone (St. Louis) hoped that the Society would make every effort to increase attendance at the annual meetings.

Dr. Irving Webber (Gainesville) requested the appointment of a representative from affiliate groups to the Council of the Society. Dr. Lansing pointed out that Dr. H. E. Jones was currently serving on the Council as the representative of affiliate groups.

Dr. Bernard Strehler (Baltimore) expressed the opin-

* A full report is available upon application to the Administrative Secretary, Mrs. Marjorie Adler, 660 South Kingshighway Boulevard, St. Louis 10, Mo.

ion that the Society should take the initiative in drawing attention to needed research in gerontology and to prepare specific research proposals. Dr. Lansing pointed out that the Sub-Committee on Biology and Medicine of the Committee on Research Grants and Fellowships was preparing a survey and making broad recommendations about needed research in gerontology. Dr. Kleemeier added that an entire inter-university project on social gerontology now in operation had been instigated by the Sub-Committee on Psychological and Social Sciences.

A unanimous vote of appreciation for the excellent organization of the annual meeting was given to the Program Committee.

There being no further business, Dr. Lansing turned the chair over to Mr. Kuplan, who expressed his appreciation of the honor and privilege of serving as President of the Society and pledged his dedication to the expansion and improvement of the activities of the Society.

The meeting adjourned at 12:45 p. m.

N. W. SHOCK, Secretary

APPLICATIONS FOR FELLOWSHIP STATUS IN GERONTOLOGICAL SOCIETY, INC. APPROVED IN 1958

SECTION ON BIOLOGICAL SCIENCES

W. G. Batt, Newark (Del.)
W. Bondareff, Bethesda
J. G. Bowne, Ames
Rebecca Gerschman, Rochester (N. Y.)
J. W. Gowen, Ames
K. Rodahl, Philadelphia
A. A. Pandazi, Milwaukee
W. B. Quay, Berkeley
G. Toro, St. Louis
E. Woodford-Williams, Sunderland, England

SECTION ON CLINICAL MEDICINE

B. M. Blum, Elkins Park (Pa.)
A. W. Brazda, Ranger (Tex.)
W. Doberauer, Vienna, Austria
D. C. Collins, Hollywood
I. Freed, New York
C. R. Joyner, Philadelphia
J. R. Kernodle, Burlington (N. C.)
P. L. Owens, Alexandria (La.)
I. B. Perlstein, Louisville
D. J. Vail, Concord
J. J. Witt, Utica

SECTION ON PSYCHOLOGICAL AND SOCIAL SCIENCES

N. W. Coppinger, Kecoughtan (Va.)
J. T. Drake, Davidson (N. Car.)
I. L. Ferguson, San Francisco
W. M. Franke, Champaign
R. W. Goshorn, Bellwood (Pa.)
K. F. Riegel, Bethesda
F. Verhage, Groningen, Holland
A. T. Welford, Cambridge, England

SECTION ON SOCIAL WELFARE

None

OFFICERS OF AFFILIATE ORGANIZATIONS AND LOCAL CHAPTERS

Western Gerontological Society

Charles A. Preuss, President (Santa Barbara)
Harold E. Jones, President-Elect (Berkeley)
Mrs. A. M. G. Russell, Secretary-Treasurer (Menlo Park)

Florida Council on Aging

Irving L. Webber, President (Gainesville)
Mrs. Margaret H. Jacks, President-Elect (Jacksonville)
Joel Hunter, Vice-President (Clearwater)
David Levine, Vice-President (Tallahassee)
L. L. Parks, Vice-President (Jacksonville)
Louis Amato, Vice-President (Fort Lauderdale)
Louise Davis, Secretary-Treasurer (Jacksonville)

Texas Society on Aging

Herbert Shore, President (Dallas)
Ernest Kiel, President-Elect (Temple)
Hiram J. Friedsam, Vice-President (Denton)
Mrs. William B. Ruggles, Secretary-Treasurer (Dallas)

INDEX TO CURRENT PERIODICAL LITERATURE

NATHAN W. SHOCK
Gerontology Branch
National Heart Institute
National Institutes of Health

THE SUBJECT categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus, most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given (*B.A.—Biological Abstracts, P.A.—Psychological Abstracts,* and *P.I.—Population Index*). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the years 1900-1933, 2nd Edition*. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Branch, Baltimore City Hospitals, Baltimore 24, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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